

Appropriate Use Criteria for Hyaluronic Acid in the Treatment of Knee Osteoarthritis in the United States

Cartilage
2017, Vol. 8(3) 234–254
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sagepub.com/journalsPermissions.nav
DOI: 10.1177/1947603516662503
journals.sagepub.com/home/CAR



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Abstract

Objective: A workgroup of clinical experts has developed an Appropriate Use Criteria (AUC) for the use of hyaluronic acid (HA) in the treatment of osteoarthritis (OA) of the knee. The increasingly broad and varied use of HA injections, lack of published clinical guidance, and limited coverage for their use has created the imperative to establish appropriateness criteria. **Methods:** The experts of this workgroup represent rheumatology, orthopedic surgery, physiatry, sports medicine, and nursing clinicians with substantive knowledge of intra-articular HA therapy. This workgroup utilized the results of a systematic review of evidence, expert clinical opinion, and current evidence-based clinical practice guidelines to develop appropriateness criteria for the use of intra-articular HA for knee OA in 17 real-world clinical scenarios. **Results:** The workgroup scored the appropriateness of treatment of each patient scenario using a 9-point scale to designate a treatment as appropriate (7-9), uncertain (4-6), or inappropriate (1-3). Six scenarios were scored as appropriate, 10 scenarios were scored as uncertain, and 1 scenario was scored as inappropriate. **Conclusion:** This article can assist clinicians in shared decision-making by providing best practices in considering HA injections for knee OA treatment. Moreover, this AUC article can aid payers and policy makers in determining reimbursement and preauthorization policies and more appropriately managing health care resources. It is clear that further research is still necessary—particularly in patient populations differentiated by OA severity—that may benefit the greatest from the use of HA injections for the treatment of knee OA.

Keywords

appropriate use criteria, hyaluronic acid, knee, osteoarthritis, viscosupplementation

Introduction

In the United States, osteoarthritis (OA) is the most common type of arthritis and joint disorder, with the knee being the most frequently involved symptomatic joint.^{1,2} OA affects millions of people and can cause significant individual disability and substantial societal costs, which continue to escalate each year.³ Additionally, the total number of total joint arthroplasty, including total knee arthroplasty (TKA), due to OA performed annually has increased and will likely continue to do so with the aging population.⁴ Estimated costs due to hospital expenditures of total knee replacements were \$28.5 billion in 2009.⁵ These joint replacement procedures are usually reserved for patients with radiographic end-stage knee OA, functionally disabling pain, and who have failed conservative treatment options.¹ However, among patients experiencing symptomatic knee OA, not all are candidates for TKA and many prefer to delay such extreme interventions as long as possible or avoid them altogether. Education, in conjunction with a multimodal approach, is usually

incorporated to treat these patients with less severe OA, including weight loss (e.g., diet, nutrition), assistive devices

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(e.g., braces, canes), physical therapy, low-impact exercise (for activity modification), nutraceuticals, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesic drugs, as well as intra-articular injections (both corticosteroid and hyaluronic acid [HA]).^{3,6,7} More recently, there has been anecdotal evidence supporting the use of platelet-rich plasma (PRP) and even stem cell injections to treat OA pain and dysfunction.^{8,9} The method of and extent to which these treatments are incorporated into the care of knee OA patients varies by patient and provider.

However, viscosupplementation—or HA injection—has gained popularity as a treatment option for the nonoperative management of patients with knee OA. The adoption of this treatment for managing pain associated with knee OA has been well documented in research performed in both cellular studies and clinical investigations.¹⁰⁻¹² Research has demonstrated that the local biology within the knee is significantly improved with HA injections, resulting in decreased pain and improved function. The mechanism of action of HA injections for joints has been studied extensively.¹³ Specifically, HA injections reduce cartilage breakdown that results from a loss of cartilage oligomeric matrix protein and also reduce inflammatory cytokines such as interleukin-1.^{14,15} A recent network meta-analysis by Bannuru *et al.* demonstrated the clinical impact of HA injections in relation to alternative pharmacologic treatments.¹⁶ The ideal result of HA injections is the potential to delay TKA. Additionally, recent studies using large administrative claims data sets have demonstrated a potential impact on knee OA and progression to TKA. Ranging from basic science to outcomes from clinical investigations, there are significant data demonstrating the positive impact of HA injections on knee OA.^{10,11,17}

Despite this positive evidence and an increasing demand for viable HA treatment options, it is important to note that many practices across the country have difficulty receiving payer authorization to treat knee OA using HA injections.^{18,19} Many payers have developed specific coverage policies that must be followed both to initiate HA injection treatment and, especially, re-treat a patient.^{18,19} Additionally, the gap in evidence-based clinical guidance for HA injection magnifies the variability and understanding of its use. In 2013, the American Academy of Orthopaedic Surgeons released their clinical practice guideline (CPG) for knee OA, which specifically recommends against the use of HA for patients with knee OA based on the systematic review of evidence used to develop this guideline.²⁰ This document reversed the Academy's previous support of HA injections, which brings the methodology used to develop its CPG recommendations into question.^{16,21} Furthermore, while scientifically rigorous, the analysis performed does not reflect the real-world impact of HA injections, particularly for disease processes with poor alternative treatments (e.g., weight loss, narcotic pain medications). Following this CPG publication, the American Academy of Orthopaedic Surgeons released their 2013 appropriate use criteria (AUC) document for non-arthroplasty treatment of knee OA, which

expressly excludes the use of HA among other therapies for which guidance is provided.²² More recently, the Agency for Healthcare Research and Quality (AHRQ) conducted a review of the evidence, which notes the use of HA in individuals with knee OA improves function, health-related quality of life, and may delay or prevent the need for knee replacement, particularly in those 65 years of age or over.²³ However, while AHRQ's publication shows a small, statistically significant effect of HA on function and relatively few adverse events, it does not offer any appropriateness criteria, and its attention to only the Medicare population fails to address the larger population of adults that may benefit most from HA therapy. Similarly, the recently published scientific statement by American Medical Society for Sports Medicine concerning viscosupplementation for knee OA presents high-level care recommendations for general use of HA injections, but does not provide guidance for specific clinical scenarios.²⁴ Additionally, there are European guidelines and consensus statements on the use of HA in the treatment of knee OA, which represent a more global perspective on this topic.^{25,26} In light of these recent publications and the sustained lack of addressing appropriate use of HA injections, this document aims to fill this gap in the literature and apply scientific evidence to inform real-world clinical scenarios.

Given the evolving health policy environment that is pushing for value, it is important to ensure that viable, safe, and efficient treatment options are available for patients who can benefit the most when they need it most. Historically, orthopedic surgeons and their physician extenders have been the primary users of HA injections. However, providers currently using HA injections for the treatment of knee OA span several additional specialties, including rheumatology, pain management, interventional psychiatry, and primary care sports medicine. As the US health care system continues to evolve and its needs change over time, there may be a shift in the profile of providers performing this type of treatment. In some parts of the country, nurse practitioners and physician assistants are more consistently providing general and nonoperative care for patients with knee OA.²⁷ Experts believe that this model of care will become increasingly necessary in the future of OA health care delivery, ultimately resulting in more injection therapy being administered by primary care providers such as internists, family medicine practitioners, and their physician extenders. This broader and varied use of viscosupplementation, along with the lack of published clinical guidance and limited coverage for its use, has created the imperative to establish appropriateness criteria.

Objective

This evidence-based AUC document seeks to increase the level of understanding of HA and its benefits in the treatment of knee OA. Furthermore, it identifies population subgroups for which HA works best and those for whom HA is

not recommended (e.g., patients with mechanical deformity). Through its guidance to providers, this article contributes a greater understanding of which patients can benefit from HA injection treatments, and it can serve to support shared decision-making among patients and providers. In this regard, patients may find value in understanding the benefit of different treatment options and how different symptoms may influence the efficacy or appropriateness of these treatments. Similarly, clinicians will benefit from the process and discovery of information regarding effectiveness and harms of HA injections for knee OA through having AUC available for use in practice.

This AUC document can assist clinicians across all specialties—including orthopedic surgeons and their health care provider extenders, rheumatologists, physiatrists, primary care sports medicine physicians, and internal medicine clinicians—in shared decision-making by providing information for best practices and can serve as guidance when considering HA injections for the treatment of knee OA. Moreover, this AUC document can be useful for payers and policy makers to determine reimbursement and preauthorization policies and to more appropriately manage scarce health care resources.

Methodology*

As mentioned, the varied use of HA injections among providers and a lack of clinical guidance to support them has created an imperative to establish appropriateness criteria. Therefore, a group of experts was convened by an independent organization, Avalere Health,[†] to address this gap in clinical guidance and develop AUC for the use of HA injections for knee OA.

Appropriate use criteria specify when it is appropriate to perform a procedure, and facilitate clinical decision-making, by combining the best available scientific evidence with the collective judgment of physicians to determine the appropriateness of performing that procedure. Unlike CPGs, which rely on a rigorous systematic review of published literature with annual review and updates to provide recommended standards of care for specific clinical conditions or procedures,²⁸ AUC are often developed for areas where evidence is lacking, making them an important resource among clinical guidance documents. When available, information on cost, cost-effectiveness of a procedure, and patient preference are also considered.

The AUC for HA in the treatment of knee OA were developed through a confidential and formalized process by a panel of diverse experts that reviewed and applied

available evidence, where applicable. The approach that follows includes descriptions of the following:

- Expert Workgroup Composition
- AUC Development
- External Document Review

Expert Workgroup Composition

The experts of this AUC Workgroup represent a multidisciplinary panel of health care providers with substantive knowledge of intra-articular HA therapy. They were selected from among several recognized health care professionals with a depth of experience treating patients with knee OA. Seven members were ultimately selected to participate in this multidisciplinary Workgroup, which included 1 rheumatologist, 3 orthopedic surgeons, 1 physiatrist, 1 primary care sports medicine physician, and 1 orthopedic nurse practitioner. Two members acted as co-chairs to provide guidance when there was discordance among the clinical opinion of the group or interpretation of the evidence reviewed. The chairs also provided initial review and feedback of the drafted document. All members contributed to the writing of this document. A complete list of Workgroup participants and external reviewers can be found in Appendix A.

Workgroup members and other key clinical leaders involved in this effort were asked to submit disclosure statements to reveal any areas of potential conflict of interest for the preceding 12 months. A signed disclosure statement was initially required of all Workgroup members before convening them, and disclosures of conflict-of-interest verbal affirmations were conducted at each teleconference and in-person meeting thereafter.

Appropriate Use Criteria Development

The process for AUC development was modeled after the RAND/UCLA Appropriateness Method for AUC development and included a systematic review of evidence to support assessment of various clinical scenarios using a modified Delphi process.^{29,30} Additionally, this process strove to adhere to the Institute of Medicine's standards for developing trustworthy clinical guidance.³¹ The process included identification of relevant clinical scenarios, a systematic synthesis of available evidence, individual and group ratings of the scenarios using a formal consensus process, and document drafting based on final group ratings and discussions.

In developing these AUC for HA injections, the Workgroup used the following definition of appropriateness to guide their considerations and group discussions: "The concept of appropriateness, as applied to health care, balances risk and benefit of a treatment, test, or procedure in the context of available resources for an individual patient with specific characteristics."³²

*Funding for this effort was provided by the Advanced Medical Technology Association (AdvaMed). AdvaMed representatives had no input regarding the scope, direction, or writing of this article.

†Avalere Health, an Inovalon Company, is a research and consulting firm dedicated to enhancing US health care.

Appropriate use criteria indications were created to represent most of the possible uses of HA injections rather than limiting the AUC to indications for which evidence was available. The resulting AUC are based on evidence and current understanding regarding technical capabilities and potential patient benefits of intra-articular viscosupplementation. Other factors affecting the AUC included potential harms (as well as long-term harms that may be difficult to capture), costs, availability, and patient preferences.

Identifying Study Scope and Parameters

The Workgroup was tasked with identifying inclusion/exclusion criteria to support key evidence questions to guide the systematic review of literature. These questions, developed in consultation with the evidence review team, addressed clinical topics for which viscosupplementation for knee OA might be considered (including situations in which it might be contraindicated). The key questions follow the population, intervention, comparison, outcome, timing, and setting

Box 1. Study Scope (PICOTS).

<p>Population:</p> <ul style="list-style-type: none"> • Patients with symptomatic osteoarthritis of the knee • Males and females • Ages 18+ • All races • All locations (rural, urban, etc.) <p>Population subgroups:</p> <ul style="list-style-type: none"> • Patients with chondral injury <ul style="list-style-type: none"> ○ Patients with intra-articular fracture who are at risk for posttraumatic arthrosis <p>Population exclusions:</p> <ul style="list-style-type: none"> • Children and adolescents (<18 years old) • Patients with diagnosis of rheumatoid arthritis • Patients with asymptomatic osteoarthritis • Patients with osteoarthritis in joints not including the knee <p>Interventions:</p> <ul style="list-style-type: none"> • Hyaluronic acid injection <ul style="list-style-type: none"> ○ Adjunct physical therapy ○ Adjunct lifestyle modifications <p>Comparisons:</p> <ul style="list-style-type: none"> • Placebo, sham injections • Corticosteroid injections • Oral anti-inflammatories • Platelet-rich plasma therapy <p>Outcomes:</p> <ul style="list-style-type: none"> • Pain <ul style="list-style-type: none"> ○ Objective measures ○ Pain on weight bearing ○ Sit-to-stand test ○ Walk test ○ Time to joint replacement ○ Outcomes measurement instruments ○ WOMAC (Western Ontario and McMaster Universities Arthritis Index) ○ KOSS (Knee Osteoarthritis Scoring System)
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(continued)

Box 1. (continued)

<ul style="list-style-type: none"> • Patient satisfaction (validated measures) • Quality of life (validated measures) • Harms <ul style="list-style-type: none"> ○ Joint infection ○ Swelling <p>Timing:</p> <ul style="list-style-type: none"> • No follow-up minimum requirement • No limitation to search start date <p>Study considerations:</p> <ul style="list-style-type: none"> • Do not limit to US studies

(PICOTS) framework for evidence questions, as established by the AHRQ.³³

The Workgroup and evidence review team carried out several iterations of this process, each time narrowing the scope of the clinical scenarios and the literature review by prioritizing the topics of interest. Box 1 provides a brief overview of the PICOTS typology used to define the key questions for this effort.

Development of Clinical Scenarios (or Indications)*

The Workgroup developed a list of clinical scenarios based on procedure scenarios and precise definitions that categorize patients in terms of their personal characteristics, symptoms, medical history, and diagnostic test results. The clinical scenarios did not address the appropriateness of other interventions for knee OA, though the systematic review did include alternative interventions as comparators. Once the systematic review of the literature was complete, the Workgroup reviewed the results and further refined the initial clinical scenarios to ensure their accuracy and facilitate consistent interpretation when scoring each indication for appropriateness. Ultimately, the Workgroup identified 17 clinical scenarios that are presented in **Table 2**.

Conducting the Systematic Review

The methods guiding this systematic review are described below. The systematic review of the relevant evidence was commissioned by an independent group, the Pacific Northwest Evidence-based Practice Center (EPC) at Oregon Health & Science University (OHSU). The primary purpose of the systematic review was to assess the effectiveness and comparative effectiveness and harms of HA injections for knee OA.

Researchers at OHSU developed the key research questions highlighted in **Table 1** to guide the systematic review using the PICOTS typology.

*The term *indication* is used interchangeably with *clinical scenario* in this document and does not imply that a procedure should necessarily be performed.

Table 1. Key Research Questions.

Key Questions	Clinical Considerations and Subquestions
<i>Question 1:</i> In adults with osteoarthritis (OA) of the knee, what is the effectiveness of hyaluronic acid (HA) versus placebo on outcomes related to pain, function, satisfaction, and quality of life?	<ol style="list-style-type: none"> How does effectiveness vary by patient subgroups (e.g., chondral injury, intra-articular (IA) fracture patients)? How does effectiveness vary by grade or stage of OA? What is the effectiveness in persons who have never received corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) previously for OA of the knee?
<i>Question 2:</i> In adults with OA of the knee, what is the comparative effectiveness of HA versus oral NSAIDs, intra-articular corticosteroids, or platelet-rich plasma therapy on outcomes related to pain, function, satisfaction, and quality of life?	<ol style="list-style-type: none"> How does effectiveness vary by patient subgroups? How does effectiveness vary by grade or stage of OA? What is the effectiveness in persons who have never received corticosteroids or NSAIDs previously for OA of the knee?
<i>Question 3:</i> In adults with OA of the knee what are the harms of HA use?	<ol style="list-style-type: none"> How do harms vary by patient subgroup? How do harms vary by grade or stage of OA? What are the harms in persons who have never received corticosteroids or NSAIDs previously for OA of the knee?
<i>Question 4:</i> In adults with OA of the knee, what is the effectiveness of HA when used as part of the multimodal approach or combination therapy on outcomes related to pain, function, satisfaction, and quality of life?	<ol style="list-style-type: none"> How does effectiveness vary by patient subgroups (e.g., chondral injury, IA fracture patients)? How does effectiveness vary by grade or stage of OA? What is the effectiveness in persons who have never received corticosteroids or NSAIDs previously for knee OA?
<i>Question 5:</i> In adults with OA of the knee, what is the effectiveness of different doses and formulations of HA on outcomes related to pain, function, satisfaction, and quality of life?	<ol style="list-style-type: none"> How does effectiveness vary by patient subgroups (e.g., chondral injury, IA fracture patients)? How does effectiveness vary by grade or stage of OA? What is the effectiveness in persons who have never received corticosteroids or NSAIDs previously for knee OA?

Searches were conducted on the following databases: the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and Ovid MEDLINE (January 1946 through May 2015). These searches were supplemented by reviewing the reference lists of relevant publications.

Extensive literature searches identified 526 citations potentially addressing the key questions of interest to this evidence review. Of those, 246 were excluded on title and abstract review for the following reasons: did not comprise a systematic review or clinical study, did not address a key question of interest to this review, did not enroll population of interest, or published prior to January 1946. A total of 280 full-length articles were reviewed. Of those, 179 were excluded at a first pass review for the following: wrong population (4), wrong intervention (39), wrong outcome (7), wrong publication type (14), wrong study design (58), included in original study (no new data) (37), foreign language (17), or paper not available (3). Overall, 100 studies addressed one or more of the key questions and were considered as evidence in this review. **Figure 1** indicates data extraction and quality assessment for included studies that addressed each of the key questions.

Two OHSU staff reviewers independently assessed the studies for inclusion and rated study quality. One reviewer abstracted data and a second reviewer checked the abstraction. The strength of overall evidence was graded as high, moderate, low, or very low using GRADE methods (based on the quality of evidence, consistency, directness, precision, and reporting bias),

in conjunction with Cochrane Back Review and AMSTAR (A Measurement Tool to Assess Systematic Reviews) to appropriately rate the strength and quality of randomized controlled trials (RCTs) and systematic reviews, respectively.

The focus of this methodology was on identifying randomized trials of adults undergoing intra-articular injections of HA to address knee OA of any duration or severity. As a result, EPC researchers included only systematic reviews and RCTs on the benefits and harms of HA compared with (1) placebo interventions, (2) specific active interventions (oral NSAIDs, intra-articular corticosteroids, or intra-articular PRP), and (3) different doses or formulations of HA (see Appendix C for a list of HA formulations). Outcomes of interest included pain, function, stiffness, knee surgery, and harms. Good- and fair-quality systematic reviews were also included, selecting those that were most relevant to the key questions and scope parameters, had the most recent search dates, and were of highest quality. (See Appendix D for quality rating criteria.) Additionally, non-English language studies and those published solely as abstracts were selected only if they were included in English-language systematic reviews.

Rating Process and Scoring

Using the evidence summary developed, Workgroup members were first asked individually to assess the benefits and risks of HA use for each of the identified clinical scenarios and provide

Table 2. Clinical Scenarios for Appropriate Use of HA Injections in Knee OA Treatment.

#	Clinical Scenario	Score
1a	Symptomatic adults with severe osteoarthritis of the knee who have clinically and radiologically confirmed disease who have not received other therapies for the knee	6 ^a (Uncertain)
1b	Symptomatic adults with moderate osteoarthritis of the knee who have clinically and radiologically confirmed disease who have not received other therapies for the knee	7 (Appropriate)
1c	Symptomatic adults with mild osteoarthritis of the knee who have clinically and radiologically confirmed disease who have not received other therapies for the knee	7 (Appropriate)
2a	Symptomatic adults with severe osteoarthritis of the knee who have clinically and radiologically confirmed disease and have failed other nonpharmacologic or pharmacologic therapies for the knee	6 ^a (Uncertain)
2b	Symptomatic adults with moderate osteoarthritis of the knee who have clinically and radiologically confirmed disease and have failed other nonpharmacologic or pharmacologic therapies for the knee	7 (Appropriate)
2c	Symptomatic adults with mild osteoarthritis of the knee who have clinically and radiologically confirmed disease and have failed other nonpharmacologic or pharmacologic therapies for the knee	7 (Appropriate)
3a	Symptomatic adults with severe osteoarthritis of the knee who have clinically and radiologically confirmed disease who have incomplete response to other therapies for the knee	6 ^a (Uncertain)
3b	Symptomatic adults with moderate osteoarthritis of the knee who have clinically and radiologically confirmed disease who have incomplete response to other therapies for the knee	7 (Appropriate)
3c	Symptomatic adults with mild osteoarthritis of the knee who have clinically and radiologically confirmed disease who have incomplete response to other therapies for the knee	7 (Appropriate)
4a	Symptomatic adults with severe osteoarthritis of the knee who are intolerant of, have a high-risk of adverse reaction to, or who are contraindicated for pharmacological agents for the knee (oral, topical, or intra-articular)	6 ^a (Uncertain)
4b	Symptomatic adults with moderate osteoarthritis of the knee who are intolerant of, have a high-risk of adverse reaction to, or who are contraindicated for pharmacological agents for the knee (oral, topical, or intra-articular)	6 ^a (Uncertain)
4c	Symptomatic adults with mild osteoarthritis of the knee who are intolerant of, have a high-risk of adverse reaction to, or who are contraindicated for pharmacological agents for the knee (oral, topical, or intra-articular)	6 ^a (Uncertain)
5	Symptomatic adults who have mechanical meniscus pathology with underlying osteoarthritis of the knee	4 (Uncertain)
6	Symptomatic adults with osteoarthritis of the knee who have had a significant adverse reaction to an intra-articular HA product	6 ^a (Uncertain)
7	Symptomatic adults with osteoarthritis of the knee who have active inflammatory arthritis (rheumatoid arthritis, gout, etc.)	4 ^a (Uncertain)
8	Symptomatic adults with osteoarthritis who have active local (periarticular) or intra-articular infection of the knee	1 (Inappropriate)
9	Symptomatic adults with osteoarthritis of the knee who have synovitis of the knee with significant effusion	5 ^a (Uncertain)

HA = hyaluronic acid; OA = osteoarthritis; AUC = appropriate use criteria.

^aAUC score that Workgroup members feel strongly can be informed by extensive clinical experience despite lack of published evidence in the literature. Please note the consensus-based rationale provided in the following sections.

an appropriateness score for each. These scores were shared with the Workgroup to use during the next phase of scoring.

Workgroup members were then convened at a daylong, in-person forum to discuss each indication and associated scores. For each indication, the mean was calculated and assigned. Following a modified Delphi approach, each member independently and anonymously provided his or her second round of scores for each indication. For each indication, the mean numerical score was determined and then assigned to the associated appropriate use category. Objective scoring was used to achieve recommendations and all Workgroup members contributed to the final discussion. Once the scoring process was completed, the final appropriate use ratings were summarized according to the RAND/UCLA Appropriateness Method.³⁰

The Workgroup scored each clinical scenario as appropriate, uncertain, or inappropriate on a scale from 1 to 9 using the following definitions:

Score 7 to 9, Appropriate: The use of the procedure is appropriate for the specific indication and is generally considered acceptable.

Score 4 to 6, Uncertain: The use of the procedure is uncertain for the specific indication, although its use may be appropriate and acceptable. Uncertainty implies that more research is needed to classify the indication definitively.

Score 1 to 3, Inappropriate: Use of the procedure is inappropriate for the specific indication and generally is not considered acceptable.

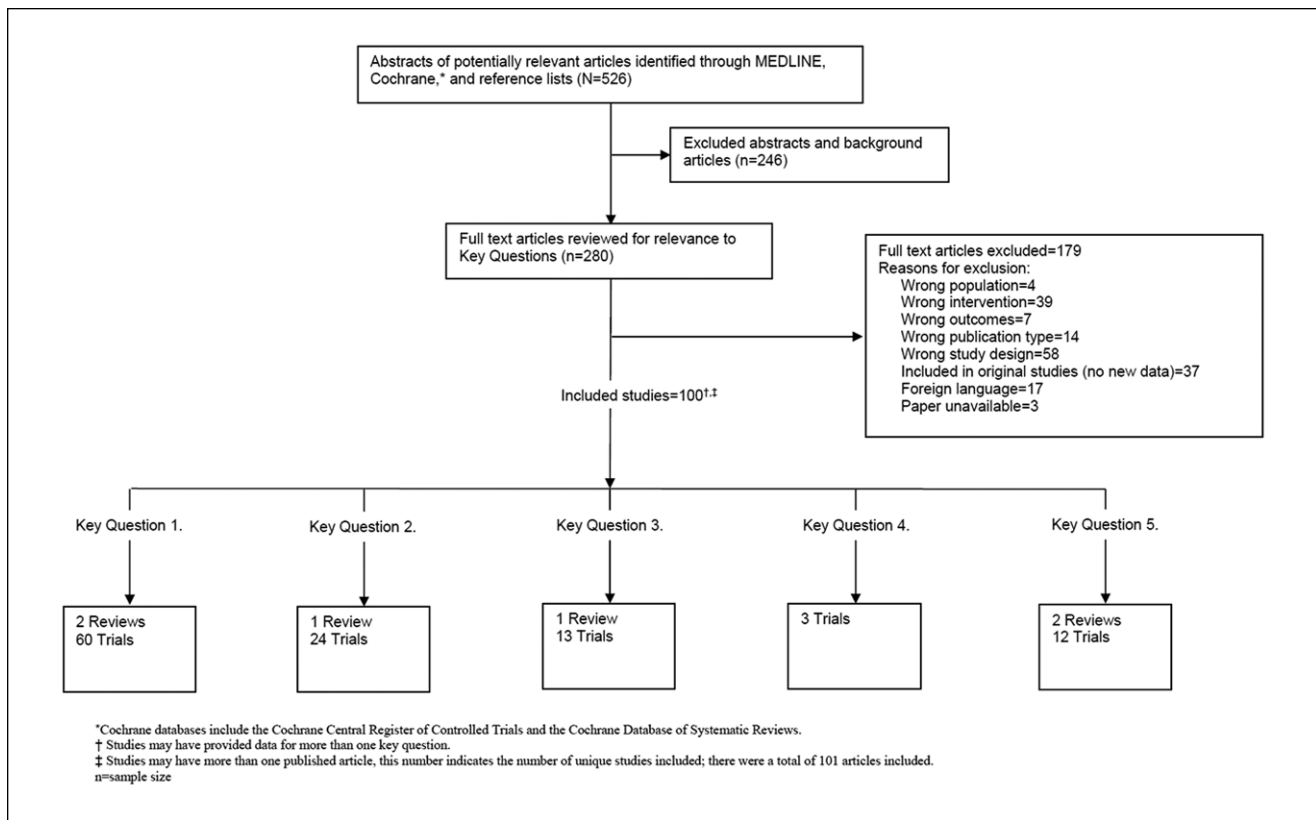


Figure 1. Literature flow diagram.

Additionally, if there was a difference in clinical opinion for a particular clinical scenario, such that Workgroup members could not agree on a common score, the co-chairs led further discussions among the members to ultimately come up with a consensus score considering the available literature and their collective clinical opinion.³⁴

External Document Review

To solicit feedback from a broader group of end users, external reviewers were asked to provide a review and critique of the initial draft of this document. Identified reviewers represented clinical professionals from varied backgrounds. (A complete list of reviewers can be found in Appendix A.) Comments and recommendations regarding proposed changes were integrated into this document as appropriate.

Clinical Background and Importance of Intra-Articular Hyaluronic Acid

Endogenous HA is essential to the integrity, health, and normal functioning of mammalian synovial fluid. Its molecular weight (MW) ranges from 2 to 10 million Daltons (Da) and it helps maintain homeostasis by

providing the necessary viscoelasticity to the synovial joint fluid.³⁵ Its properties change based on the stress that the joint is placed under at any given time. HA facilitates both lubrication and elasticity of the joint cartilage. Low-impact activities that produce a shear stress across the joint utilize the lubricating properties of HA, whereas high-impact movements that generate compressive forces on a healthy joint benefit from the shock absorption properties of HA.³⁶⁻⁴⁰ Furthermore, with inflammation, HA may offer protective properties to the joint tissue by scavenging free radicals and reducing oxidative damage.³⁵

As OA naturally progresses, the properties of the HA within the joint change. The concentration and MW of the synovial fluid HA molecules decrease, thereby diminishing the viscoelastic, protective properties this fluid offers to the joint cartilage in times of increased stress.^{35-37,41-43} It is this recognized phenomenon of naturally diminishing HA properties over time that led to the concept of utilizing purified exogenous HA for OA of the joints, particularly the knee, to potentially reduce pain and improve function. Since its development, exogenous HA (intra-articular HA injection) has been in clinical use worldwide for decades.^{44,45} However, its exact mechanism of action is unclear and appears to be multifactorial.

Benefits of Hyaluronic Acid Interventions

Injected HA's main functions stem from its antinociceptive properties, ability to improve the viscoelastic properties of synovial fluid, and indirect lubrication of the joint through stimulated endogenous HA synthesis.^{35,36} Other potential anecdotal benefits of HA injections that have been proposed include chondroprotection and potential function as a disease-modifying agent for OA.^{35,36,46} More specifically, Type II collagen degradation products appear to be a marker of cartilage degradation and OA disease activity. HA has been shown to protect against this degradation in articular chondrocytes.^{47,48} It is also suggested HA injections may delay TKAs.⁴⁹

HA injection products for treating knee OA pain have been approved for use in the United States since 1997. Since then, several HA viscosupplementation products have come to the US market differing in MW (high vs. low), source (avian vs. bacterial fermentation), origin (purified hyaluronan vs. cross-linked hylan), concentration, and volume.⁵⁰ They have become an essential component of the multimodal knee OA treatment algorithm that many clinicians utilize in practice on a daily basis.⁵¹ The majority of studies that have been performed focus on HA injection use with mild to moderate OA of the knee joint, indicating a tendency to use exogenous HA earlier rather than later in the course of treatment.

The use of HA injections can minimize that of intra-articular steroids, which, if used repeatedly and frequently over time, may cause additional damage to the articular joint cartilage.^{17,40} Additional benefits of HA injections include longer duration (average 6 to 8 months) of benefit and overall safety profile when compared with intra-articular steroids.^{17,40} However, in acute OA flare-ups, especially those with a joint effusion, intra-articular steroids can have a very positive effect and should be considered over HA injections.^{17,40} The 2 types of injections can often be used in synergy to treat knee OA depending on the patient.

These HA products are frequently given as a multi-injection series, though more recently, single injection HA products have become available. Each type (single vs. multi-injection) offers different advantages and disadvantages that need to be considered on an individual basis when treating knee OA patients. Single injections offer the convenience of a onetime office visit, fewer needle sticks, a lower risk of infection, and reduced injection site pain and tissue trauma, as well as potential cost savings for the patient and insurance company. However, multi-injection HA series can offer the benefit of improved efficacy in pain relief and increased provider visits to receive more education and guidance in treating the patient's knee OA. Furthermore, the clinician can monitor more closely how the patient is responding to the injections over a multi-week period.

Most patients require retreatment with HA injections over a 6- to 8-month period. The option to re-treat is based on a clinical assessment of the patient and his/her overall response to prior HA treatments. It is imperative to develop treatment and re-treatment guidelines within one's clinical practice, and each patient's care must be individualized. The time-frame of benefit from HA injections varies, but on average most patients can achieve results for up to 2 years, sometimes longer.⁹

Potential Harms of Hyaluronic Acid Interventions

Adverse effects with HA injections are usually minimal with the most frequent postinjection complaints of injection-site pain, joint stiffness, and possibly swelling being short-lived (1 to 2 days).⁵²⁻⁵⁵ These are usually treated conservatively with ice, NSAIDs, and relative rest. More severe adverse effects (i.e., pseudoseptic reaction, granulomatous reactions, pseudogout) are uncommon but tend to be a higher risk with hylan more so than with hyaluronan products. Furthermore, avian-based products have the potential to elicit more adverse allergic reactions than non-avian-based preparations.^{52,53}

Indications and Appropriate Use Criteria Scores

Supported by the HA treatment options outlined above, clinicians are often faced with variability in the efficacy of these treatments. In the context of failed or ineffective previous treatments among OA patients, providers typically seek other options to improve the patient's condition or symptoms, even when little evidence of an effective alternative treatment is available.

To understand the role of HA injection use among other available therapies, a systematic review was conducted to assess the effectiveness, and comparative effectiveness and harms of HA injections for knee OA.

Summary of the Evidence

Of the 526 studies identified through an initial literature search, 100 studies (systematic reviews and randomized trials) were ultimately selected. Among those 100 studies, a network meta-analysis of good-quality studies found HA injections to be superior to intra-articular placebo for improving pain (standardized mean difference [SMD] 0.34, 95% credible interval [CrI] 0.26 to 0.42) and function (SMD 0.30, 95% CrI 0.20 to 0.40) in patients with knee OA.¹⁶ Effects averaged less than 10 points on a 0 to 100 pain scale at 3-month follow-up and there were no differences in risk of any adverse event, serious adverse events, withdrawal due to adverse events, or local reactions.

In that same network meta-analysis, HA injection performed better or was similar to other pharmacological therapies and did not appear to be associated with more harms than intra-articular placebo.¹⁶ HA injection was more effective than oral NSAIDs in improving pain and function, though effects were somewhat smaller in magnitude than observed for intra-articular HA versus intra-articular placebo.¹⁶ There were no clear differences between HA injection versus intra-articular corticosteroids in improvement in pain, though HA injections were associated with small beneficial effects on function; HA injection was associated with similar safety when compared with intra-articular corticosteroids.¹⁶ Trials of HA versus PRP reported inconsistent results and most had methodological shortcomings, but the highest quality trial found no overall differences between HA versus PRP in WOMAC function, and favored PRP only in a subgroup of patients with Kellgren-Lawrence (K-L) grade 0 to 2 OA.⁵⁶ Of the 2 trials that evaluated effects of HA injections on the risk of surgery, results favored HA injections but differences were not statistically significant.^{57,58}

Evidence was too limited to determine how effects of HA injections vary in subgroups characterized by baseline OA severity, presence of chondral injury or intra-articular fracture, and receipt of NSAIDs or prior corticosteroid injections. With regard to baseline OA severity, almost all trials enrolled a spectrum of patients that included moderate OA (grades II or III). Trials that stratified results according to baseline OA grade reported somewhat conflicting findings. It was unclear in most cases if the subgroup analyses were prespecified or post hoc and statistical tests for an interaction were generally not reported. Limited evidence from 2 trials that focused on patients with grade I or II OA found no difference between intra-articular HA and intra-articular saline as a placebo.^{59,60} In one of the trials, HA therapy was associated with beneficial effects in a subgroup of older patients with higher Lequesne index scores at baseline.⁵⁸ The only trial to focus on patients with grade IV OA found HA injections superior to placebo in WOMAC scores, but the trial was small and had methodological shortcomings.⁵⁷ With regard to presence of chondral injury, intra-articular fracture, or prior therapies, these patients were excluded from participation in most trials. Few trials reported the proportion of patients with these characteristics and no trial reported effects in subgroups defined by presence of these factors.⁶⁰⁻⁶²

Evidence to determine the optimal number of injections or dose was also insufficient. Few trials directly compared different numbers of injections or different doses, and the dosing regimen and dose comparisons varied among the trials available. However, one systematic review did identify a trend toward larger effects in trials that evaluated 1 to 3 injections than in those that evaluated more than 3 injections (although the test for an interaction effect was only slightly above the threshold for statistical significance).⁶³ There were no clear differences

identified between different HA formulations based on MW or use of cross-linking in a systematic review and subsequent head-to-head trials.^{63,64}

Overall, it was found that HA is more effective than intra-articular saline as a placebo, but that its impact on pain and overall function is relatively limited. When compared with active treatments, effects were smaller or there were no clear differences. More evidence is needed to determine how effects of HA vary according to OA grade, receipt of prior treatments, dose, formulation, and presence of chondral injury or intra-articular fracture. Because all HA preparations utilize saline as a diluent, any trials comparing intra-articular HA to intra-articular saline are truly examining whether HA and saline is better than saline alone.

Workgroup Discussions of the Evidence

Although the evidence on HA effectiveness is limited, the Workgroup recognized that there is an increasing need to consider HA injections as a primary therapy given the expected rise in prevalence of knee OA among US adults. It is currently estimated that 1 in 2 people may develop symptomatic knee OA by 85 years of age, and an effective therapeutic program becomes more important as the population ages and the burden of disease increases.⁶⁵ As previously mentioned, no single care treatment program serves all purposes and patient regimens must be properly individualized. Presently, therapeutic guidelines rate the relative importance of a treatment but, in general, lack specificity as to when a therapy is appropriate.

As presented in the summary of evidence above, the literature reviewed by this Workgroup indicates that HA injection therapy is as effective as other therapies for knee OA.¹⁶ Indeed, in the clinical setting there is an increase in the use of intra-articular HA, perhaps reflecting the unmet need for symptom relief in the aging population with knee OA, the increasing prevalence of joint replacement, and the associated cost in an increasingly restricted budget for health care.⁶⁶ It is important to note that clinical trials, by nature, study restricted populations and do not differentiate among stages of clinical care, such as grades of knee OA. Hence, existing clinical guidance does not offer subsets of recommendations for patient care. In addition, the evidence review did not include studies specific to the anatomy of the knee; however, all studies examined the effects of global knee OA. As a result, the AUC scores provided encompass recommendations for all types of knee OA (e.g., patellar).

For these reasons, this Workgroup utilized the existing literature supplemented with expert opinion to develop appropriateness criteria for the use of intra-articular HA for knee OA in specific clinical scenarios. The workgroup clinically defines knee OA by radiographic severity, not by patient symptoms or pain, using the K-L grading scheme.⁶⁷

- *Grade 0*: No radiographic features of OA are present
- *Grade 1*: Doubtful joint space narrowing (JSN) and possible osteophytic lipping
- *Grade 2*: Radiographic OA, as evident by the presence of definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph
- *Grade 3*: Multiple osteophytes, definite JSN, sclerosis, possible bony deformity
- *Grade 4*: Large osteophytes, marked JSN, severe sclerosis, and definite bony deformity

These aforementioned clinical scenarios are presented in **Table 2** and reflect this Workgroup's professional and expert knowledge regarding most common patient conditions for which HA injections may be considered.

Evidence and Rationale Supporting Appropriate Use Criteria Scores

This Workgroup recognizes that each clinical scenario (**Table 2**) and resulting treatment is unique to each individual patient. Therefore, the clinical scenarios developed are intended to be as representative of the affected patient population as possible, with the recognition that a patient's specific condition and situation, coupled with a provider's individual clinical judgment, may lead them to differing conclusions for treatment.

Scoring Evidence and Rationale: Clinical Scenarios 1a to 1c

Knee OA is generally treated using a multimodal approach including both nonpharmacological and pharmacological programs that are tailored to meet individual patient's needs. There are several studies in the literature comparing HA injection to saline as a "placebo" for mild, moderate, and severe OA.^{68,69} Many of these studies support the positive impact of HA treatment with reduction of pain and stiffness in the knee. The group agreed to an evidence-based score of 7 from supporting literature that HA injections are an appropriate first-line treatment for patients confirmed to have mild or moderate knee OA who have not received other therapies for the knee. Unfortunately, there is limited evidence available that evaluates HA on patients with severe knee OA. However, as evident in the study conducted by Blanco *et al.*, HA injections for severe knee OA was found useful.⁵⁷ Therefore, the group agreed to an evidence-based score of 6 for patients confirmed to have severe knee OA. Several of these studies had limited information on simultaneous or prior trials of other nonpharmacological and/or pharmacological programs in addition to HA treatment. Additional research is needed that better assesses the impact and outcome of HA treatment on patient populations with severe knee OA.

Scoring Evidence and Rationale: Clinical Scenarios 2a to 2c and 3a to 3c

Patients may present with symptoms of knee OA after having tried one or more treatments, either on their own or from another provider. It is unclear as to how prior treatments affect the usefulness of HA injections and whether results may vary by disease severity. Unfortunately, the design of many studies reviewed by this Workgroup makes it difficult to answer these questions. No studies actively enrolled patients with recent non-HA treatment and assessed their response to HA as a function of another failed or inadequate treatment. Additionally, in most studies, patients underwent a pretreatment "washout period" where the impact of other treatment options were excluded.⁷⁰⁻⁷² Thus, the impact of HA injections in patients who have failed other treatment options would not be able to be identified. However, because of the washout periods it can be assumed that such patients were included in some capacity in those studies, making the study outcomes equally applicable to those patient populations.

Similar to the varying impact of previous treatments, patients with varying severity of disease often have differing responses to treatments. Certain treatments are more or less effective based on OA severity and, when coupled to other previous treatments, the impact of one specific treatment can be confounded. Unfortunately, among patients who have failed or have an inadequate response to various nonsurgical treatments, there are no randomized trials that assess the effectiveness of HA injections by disease severity, let alone in the context of failed non-HA treatments. Nonetheless, the Workgroup reviewed numerous studies that compared HA injections with placebo in isolated disease severity populations including trials with mild, mild-moderate, moderate-severe, and severe OA. In comparing studies of isolated disease severity the evidence suggests that patients with mild to moderate knee OA would benefit from HA intervention.^{57,58} However, there were insufficient data to determine the benefit for patients with severe knee OA. As a result, the Workgroup agreed that the evidence sufficiently supports an appropriate score of 7 for Clinical Scenarios 2b, 2c, 3b, and 3c, which represent patients with mild and moderate knee OA with a failed or incomplete response to previous nonsurgical treatment. However, the evidence was insufficient for patients with severe OA; hence, the uncertain score of 6 for Clinical Scenarios 2a and 3a.

Despite the uncertain scores attributed to Clinical Scenarios 2a and 3a, based on available published literature, the collective experience of the Workgroup suggests that use of HA injections among these patients often has beneficial outcomes. Improved outcomes among these patients is less frequent than those with mild or moderate OA, but is a

viable treatment consideration, particularly in light of failed or incomplete treatments.

Scoring Evidence and Rationale: Clinical Scenarios 4a to 4c

As discussed previously, treating knee OA consists of a multimodal approach including nonpharmacologic and pharmacologic treatments. Treatment options become limited for individuals with restrictions on exercise due to cardiovascular, neurologic, or other conditions. Additionally, treatment options are limited when an individual cannot or should not use pharmacologic agents due to a prior adverse reaction, a high risk of an adverse reaction, or if there is a specific contraindication. Examples might include NSAIDs, peptic ulcer disease, risk or presence of cardiovascular disease, borderline or reduced renal function, concomitant use of NSAIDs and an anticoagulant, aspirin-sensitive asthma, risk of drug abuse. Unfortunately, there are no clinical trials that evaluate intra-articular HA directed in these specific situations. However, as discussed elsewhere, there are studies that demonstrate that intra-articular HA is somewhat superior to intra-articular saline in clinical trials of subjects, most who do not have the above restrictions.⁶⁸ Hence, the group agreed to an evidence-based score of 6 for the use of intra-articular HA with restrictions on alternative treatments.

For these clinical scenarios, however, the Workgroup notes that according to their collective clinical experience, because of the restricted options these patients may have for managing their conditions, they would recommend consideration of HA injection therapy. Workgroup members have found that these patients often respond particularly well to HA injections; therefore, HA injections may be a more appropriate therapy than indicated by the available literature. More research is needed to confirm or validate these findings.

Scoring Evidence and Rationale: Clinical Scenario 5

Long-term outcomes of either arthroscopic or conservative treatment provide similar results for most patients who have mechanical meniscus pathology with underlying knee OA.⁷³ More studies with short- and long-term outcomes are needed to see if arthroscopy is superior to conservative management including use of HA as well NSAIDs and physical therapy.⁷⁴ Thus, there is no clear consensus as to which is the better approach for this subgroup. Current expert opinion is also divided among specialists treating knee OA, with physiatrists, primary care sports medicine physicians, and rheumatologists preferring conservative treatment and orthopedic surgeons preferring the surgical route. Therefore, the group agreed to an evidence-based score of 4 for patients with mechanical meniscus pathology and underlying knee OA.

Scoring Evidence and Rationale: Clinical Scenario 6

The most common adverse reaction to intra-articular HA is transient injection site pain. This is transient and requires no intervention or change in therapy. A more severe adverse reaction is an acute synovitis that occurs within a few days of injection and is most commonly reported with the cross-linked HA products. Despite its appearance, it is not due to infection, hence the terminology “pseudo-septic reaction.” The Workgroup feels that symptomatic adults who have knee OA and who have had an adverse reaction to cross-linked HA products may benefit from trying a different non-cross-linked product. Repeated injections of cross-linked HA has been reported to cause granulomatous inflammation.⁷⁵ In addition, even without the acute inflammatory response, cross-linked HA has been shown to increase effusion-related side effects.⁷⁶ This group strongly agreed that a reaction to cross-linked HA products should lead the clinician to switch to non-cross-linked HA products. To our knowledge, non-cross-linked products have not been reported to have this type of inflammatory reaction. In comparing avian and non-avian HA treatments, there was a significantly greater number of adverse events (4.8 vs. 1.7; $P < 0.01$) with avian products.⁷⁷ However, the literature review found no clear difference in overall effectiveness in decreasing pain between cross-linked and non-cross-linked HA products, higher versus lower molecular weight HA formulations, or avian versus non-avian products.^{63,64,77} Therefore, the Workgroup members recommend the trial of another HA product, considering carefully the risk versus benefit ratio for the patient. Given this assessment, the Workgroup agreed to an evidence-based score of 6 for patients who have had a significant adverse reaction to another intra-articular HA product.

Scoring Evidence and Rationale: Clinical Scenario 7

In certain circumstances, symptomatic adults with knee OA may have active inflammation from a concomitant arthritic condition. Unfortunately, there is minimal evidence on which to base treatment with HA injections, and evidence that treatment with HA as a first-line treatment is inappropriate.^{60,78} Therefore, the group agreed to an evidence-based score of 4 and suggests that injection with a corticosteroid is the most appropriate initial step in treatment for a patient with known knee OA and active noninfectious inflammatory arthritis.

Scoring Evidence and Rationale: Clinical Scenario 8

Despite the lack of evidence in the literature, the group agreed that HA injections are contraindicated in any patient with a local skin infection at the site of injection and/or an active joint infection. The group’s evidence-based score of 1

reaffirms expert opinion regarding the unacceptable use of HA injections in such a clinical scenario. Such patients should have these local skin infections and/or joint infections treated expeditiously using an aggressive, efficient, and systematic treatment approach. This may require incorporating antibiotics, repeated joint aspiration, and/or potentially arthroscopic lavage of the joint. However, the group also felt that HA injections could ultimately be utilized in these patients, if appropriate, once the infection was *completely* resolved.

Scoring Evidence and Rationale: Clinical Scenario 9

Symptomatic adults with knee OA may present with synovitis and significant effusion. There are limited data on the use of intra-articular HA in this population. Additional research should be conducted to clarify this indication and help define precisely what constitutes a significant effusion. Nonetheless, the group agreed to an evidence-based score of 5 in that conditional use of HA injections in this situation could be appropriate given the right conditions (i.e., effusion related to OA only) and inappropriate under the wrong conditions (i.e., effusions related to active inflammatory arthropathies or joint infections). Assuming these patients do not have an active local skin infection, joint infection, and/or active inflammatory condition (i.e., inflammatory arthropathies), their effusion would have to be aspirated prior to injecting any HA products in order to maximize effectiveness. However, these procedures could be performed concurrently with only one needle stick, if done correctly, using sterile technique. Some patients may benefit from an initial aspiration and injection with an intra-articular steroid prior to using an HA product to maximize its benefit. This group felt it was appropriate to perform such a procedure and allow a week or two for the steroid to positively affect the synovitis/effusion prior to injecting the HA product. If utilized in the right clinical scenario, the use of HA injections in these patients could be both appropriate and acceptable.

Qualifying Statements

Limitations

Significant limitations were identified in writing this AUC document. Defining real-world clinical scenarios for which to determine appropriate use exposes the existing weakness of the current literature. The AUC process involves the use of a rating system that is based on substantiation with published research. Currently, there is a paucity of studies that include patients with grade I OA. Most studies include patients with grade II or III OA; therefore, the evidence in the existing literature is too limited to determine the effectiveness of treatment with HA in

patients with grade I disease. Additional subsets of patients are also missing from the evidence provided in the available literature. Clinically, there are patient subsets that the expert opinion agrees would be ideal candidates for the use of HA injections (i.e., patients with OA who have comorbid conditions that prevent them from taking NSAIDs, injections, or other forms of treatment). However, there are limited high-level research studies designed specifically to examine those patient populations. This illustrates how the limitations in the existing scientific literature may cause these AUC to fail to represent the practical clinical use of HA as a treatment modality. Additional research is needed to investigate the use of HA in the patient populations who present with either chondral injury or intra-articular fracture. This population theoretically and anecdotally may benefit from the use of HA; however, current studies have not specifically focused on this subgroup. Finally, this document represents the perspectives of US clinicians on the AUC for intra-articular HA in the treatment of knee OA.

Discussion

Because clinical decision-making is multifactorial, variables taken into consideration should include clinician experience, patient preferences, and risk-benefit ratios, each of which needs to be weighed on an individual basis. The AUC provided in this article can assist clinicians by facilitating a discussion with their patients and by serving as a guideline for the treatment of the individual. Nonetheless, as evidenced by the discovery process for work regarding this AUC, it is clear that further research is necessary. A particular area earmarked for research would be to identify specific patient populations—including differentiating among grades of OA severity—that may benefit the greatest from the use of HA injections for the treatment of knee OA.

Implementation of This Guidance

Implementation of an AUC guideline document is always a difficult task. Multiple facets of clinical care regarding the specific focus of the AUC need to be considered at great length. Most important, one must consider the clinical implication of the guidance and how it can be incorporated into an appropriate treatment algorithm for the use of HA injections for knee OA. A primary goal of this AUC article is to educate and guide not only clinicians but also payers and other stakeholders regarding the use of HA injections for knee OA and when its use may be most beneficial. To this end, determining the appropriate time to incorporate HA injections in a patient's treatment plan is critical for good patient care. Based on the information that has been presented, HA injections play a

positive role in the treatment of knee OA, particularly earlier in the progression of the condition. But more large-scale, outcome-based studies need to be performed to enhance current knowledge and favorability of using HA for treating knee OA. The changing landscape of medicine will clearly focus and put more value on these outcome-based studies to complement the clinical care of

patients. While this AUC document stands to validate expert opinion, each practitioner will need to individualize his/her clinical care of a particular patient with knee OA depending on the clinical situation. Stakeholders can rely on these AUC as a foundation on which to build and help direct clinical and policy decision-making for the use of HA treatment.

Appendix A

Acknowledgements and Conflicts of Interest

The following individuals reviewed and provided feedback on this document prior to submission.

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The authors declare the following conflicts of interest.

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Appendix B

Clinical Scenarios for Appropriate Use of Hyaluronic Acid (HA) Injections in Knee Osteoarthritis (OA) Treatment, Categorized by Level of OA Severity.

#	Clinical Scenarios for Severe OA	Score
1a	Symptomatic adults with severe osteoarthritis of the knee who have clinically and radiologically confirmed disease who have not received other therapies for the knee	6 ^a (Uncertain)
2a	Symptomatic adults with severe osteoarthritis of the knee who have clinically and radiologically confirmed disease and have failed other non-pharmacologic or pharmacologic therapies for the knee	6 ^a (Uncertain)
3a	Symptomatic adults with severe osteoarthritis of the knee who have clinically and radiologically confirmed disease who have incomplete response to other therapies for the knee	6 ^a (Uncertain)
4a	Symptomatic adults with severe osteoarthritis of the knee who are intolerant of, have a high-risk of adverse reaction to, or who are contraindicated for pharmacological agents for the knee (oral, topical, or intra-articular)	6 ^a (Uncertain)
#	Clinical Scenarios for Moderate OA	Score
1b	Symptomatic adults with moderate osteoarthritis of the knee who have clinically and radiologically confirmed disease who have not received other therapies for the knee	7 (Appropriate)
2b	Symptomatic adults with moderate osteoarthritis of the knee who have clinically and radiologically confirmed disease and have failed other nonpharmacologic or pharmacologic therapies for the knee	7 (Appropriate)
3b	Symptomatic adults with moderate osteoarthritis of the knee who have clinically and radiologically confirmed disease who have incomplete response to other therapies for the knee	7 (Appropriate)
4b	Symptomatic adults with moderate osteoarthritis of the knee who are intolerant of, have a high-risk of adverse reaction to, or who are contraindicated for pharmacological agents for the knee (oral, topical, or intra-articular)	6 ^a (Uncertain)
#	Clinical Scenarios for Mild OA	Score
1c	Symptomatic adults with mild osteoarthritis of the knee who have clinically and radiologically confirmed disease who have not received other therapies for the knee	7 (Appropriate)
2c	Symptomatic adults with mild osteoarthritis of the knee who have clinically and radiologically confirmed disease and have failed other nonpharmacologic or pharmacologic therapies for the knee	7 (Appropriate)
3c	Symptomatic adults with mild osteoarthritis of the knee who have clinically and radiologically confirmed disease who have incomplete response to other therapies for the knee	7 (Appropriate)
4c	Symptomatic adults with mild osteoarthritis of the knee who are intolerant of, have a high-risk of adverse reaction to, or who are contraindicated for pharmacological agents for the knee (oral, topical, or intra-articular)	6 ^a (Uncertain)
#	Clinical Scenarios for General OA	Score
5	Symptomatic adults who have mechanical meniscus pathology with underlying osteoarthritis of the knee	4 (Uncertain)
6	Symptomatic adults with osteoarthritis of the knee who have had a significant adverse reaction to an intra-articular HA product	6 ^a (Uncertain)
7	Symptomatic adults with osteoarthritis of the knee who have active inflammatory arthritis (rheumatoid arthritis, gout, etc.)	4 ^a (Uncertain)
8	Symptomatic adults with osteoarthritis who have active local (periarticular) or intra-articular infection of the knee	1 (Inappropriate)
9	Symptomatic adults with osteoarthritis of the knee who have synovitis of the knee with significant effusion	5 ^a (Uncertain)

^aAUC score that Workgroup members feel strongly can be informed by extensive clinical experience despite lack of published evidence in the literature. Please note the consensus-based rationale provided in the text.

Appendix C

Formulations of Hyaluronic Acid Products.

Drug Name	Availability	Molecular Weight (Da)	Dosage	Injections	Generic Name
Euflexxa (formerly Nuflexxa)	FDA-approved	2.4-3.6 million	20 mg/wk	3	Sodium hyaluronate
Gel-One	FDA-approved	Undetermined	30 mg	1	Cross-linked hyaluronate
Hyalgan	FDA-approved	500-730 thousand	30 mg/wk	5	Sodium hyaluronate
Monovisc	FDA-approved	Undetermined	88 mg	1	Hyaluronan
Orthovisc	FDA-approved	1.7-2.9 million	30 mg/wk	3-4	Hyaluronan
Supartz FX	FDA-approved	620 thousand-1.17 million	25 mg/wk	5	Sodium hyaluronate
Synvisc	FDA-approved	7 million + gel	16 mg/wk	3	Cross-linked hylan G-F 20
Synvisc-One	FDA-approved	6 million + gel	48 mg	1	Cross-linked hylan G-F 20
Durolane	Canada, Europe, Australia, Others	Undetermined	20 mg	1	Stabilized hyaluronic acid
Suplasyn	Canada, Europe	500-750 thousand	20 mg	3	Sodium hyaluronate
Artz	Japan, United States, China, Europe	600 thousand-1.2 million	25 mg	3-5	Sodium hyaluronate
Suvenyl	Japan	1.8-2 million	25 mg	5	Sodium hyaluronate
Adant	Europe, Asia, Latin South America	600 thousand-1.2 million	25 mg	3-5	Sodium hyaluronate
Arthrum H	Europe	2 million	40 mg	3	Sodium hyaluronate
Arthrum Single Injection	Europe	2.8 million	75 mg	1	Sodium hyaluronate
Ostenil	Europe	1.2 million	20 mg	3-5	Sodium hyaluronate
ViscornealOrtho	France	Less than 6 million	20 mg	3	Sodium hyaluronate
Artzal (Supartz)	Sweden, Finland, Iceland, Austria	Undetermined	30 mg	5	Sodium hyaluronate
Nuflexxa	FDA-approved	2.4-3.6 million	20 mg	3	Sodium hyaluronate
Fermathron	Europe, Brazil	1 million	20 mg	3-5	Sodium hyaluronate
Go-On	Europe	Undetermined	Unknown	5	Sodium hyaluronate and sorbitol
Sinovial	Europe	1.1 million	16.8 mg/wk	3	Sodium hyaluronate
Gelsyn-3	FDA-approved	1.1 million	16.8 mg/wk	3	Sodium hyaluronate

FDA = US Food and Drug Administration.

Appendix D

Quality Rating Criteria Used for Systematic Review.

Systematic Reviews⁷⁹

Criteria:

- Was an "a priori" design provided?
- Was there duplicate study selection and data extraction?
- Was a comprehensive literature search performed?
- Was the status of publication (i.e., grey literature) used as an inclusion criterion?
- Was a list of studies (included and excluded) provided?
- Were the characteristics of the included studies provided?
- Was the scientific quality of the included studies assessed and documented?

(continued)

Appendix D (continued)

- Was the scientific quality of the included studies used appropriately in formulating conclusions?
- Were the methods used to combine the findings of studies appropriate?
 - Do qualitative synthesis and Strength of Evidence ratings appropriately consider factors such as precision, consistency, and methodological limitations?
- Was the likelihood of publication bias assessed?
- Were conflicts of interest described for the systematic review authors?
- Were conflicts of interest described for authors of the primary studies?

Response options for all questions*: Yes, no, unclear, or not applicable

Definitions of ratings based on above criteria:

Good: Meets all criteria: Reports comprehensive and reproducible search methods and results; reports pre-defined criteria to select studies and reports reasons for excluding potentially relevant studies; adequately evaluates quality of included studies and incorporates assessments of quality when synthesizing data; reports methods for synthesizing data and uses appropriate methods to combine data qualitatively or quantitatively; conclusions supported by the evidence reviewed.

Fair: Studies will be graded fair if they fail to meet one or more of the above criteria, but the limitations are not judged as being major.

Poor: Studies will be graded poor if they have a major limitation in one or more of the above criteria.

Randomized Controlled Trials (RCTs)

When included in an included systematic review:

- We used the quality ratings or risk of bias assessments as performed in the systematic reviews, as long as they used a standardized method for assessing quality (e.g., Cochrane Back Review Group, Cochrane Risk of Bias tool, PEDro scale).

When not included in a systematic review⁸⁰:

Initial assembly of comparable groups

- Was randomization adequate?
- Was allocation concealment adequate?
- Were groups similar at baseline?
- Was eligibility criteria specified?

Maintenance of comparable groups

- Was attrition and withdrawal reported?
- Was attrition acceptable and comparable between groups?
- Were patients analyzed in the groups in which they were randomized?

Measurements: equal, reliable, and valid

- Were outcome assessors masked?
- Were care providers masked?
- Were patients masked?

Important outcomes considered

- Was the primary outcome specified in the report?

Response options for all questions*: Yes, no, unclear, or not applicable

Definitions of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis. Intention to treat analysis is used.

Fair: Studies will be graded “fair” if any or all of the following problems occur, without the fatal flaws noted in the “poor” category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is used.

Poor: Studies will be graded “poor” if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention to treat analysis may be lacking.

*Additional details added when applicable.

Appendix E

Glossary of Relevant Clinical Terms.

*Arthritis*⁸¹—The inflammation of one or more joints

*Arthroscopy*⁸²—A form of minimally invasive surgery in which a fiber-optic camera, the arthroscope, is introduced into an area of the body through a small incision

*Arthroscopic lavage*⁸³—Visually guided introduction of saline solution into the knee joint and removal of fluid, with the intent of extracting any excess fluids and loose bodies that may be in the knee joint

*Articular cartilage*⁸²—A smooth, glistening surface that covers the ends of bones that articulate with each other to form a joint

*Aspiration*⁸²—Removal of fluids from a body cavity; often done to obtain specimens for analysis

*Cartilage oligomeric matrix protein*⁸⁴—Non-collagenous extracellular matrix protein expressed primarily in cartilage, ligament, and tendon

*Chondral injury*⁸⁵—Injuries to, or loss of, the articular cartilage that exposes the underlying “subchondral” bone surface

*Chondroprotective*⁸⁶—Substance that protects articular cartilage during the course of osteoarthritis

*Corticosteroids*⁸⁷—A group of hormones, including cortisol, which are produced by the adrenal glands. Some regulate the body’s fluid balance; others influence the body use of fat and sugar (glucose). Corticosteroids can be synthetically produced and have powerful anti-inflammatory effects.

*Cytokines*⁸⁸—Any of numerous hormone-like, low-molecular-weight proteins, secreted by various cell types that regulate the intensity and duration of immune response and mediate cell-cell communication

*Effusion*⁸²—Intra-articular swelling

*Hyaluronate*⁸⁹—Similar to a substance that occurs naturally in joints and that helps joints work properly by acting like a lubricant and shock absorber; injected directly into the knee to relieve pain caused by osteoarthritis

*Hylan (Hylan G-F 20)*⁹⁰—Elastoviscous high-molecular-weight fluid containing hylan polymers (derivatives of hyaluronan or sodium hyaluronate) produced from chicken combs

Hyaluronic acid or Hyaluronan^{88,91}—Mucopolysaccharide made up of alternating β1,4-linked residues of hyaluronic acid, forming a gelatinous material in the tissue spaces and acting as a lubricant and shock absorber generally throughout the body; belongs to disease-modifying antirheumatic drug class. It is important to distinguish between naturally occurring, or endogenous, HA, as well as manufactured, or exogenous HA.

*Interleukin*⁸⁸—Group of multifunctional cytokines once their amino acid structure is known

*Intra-articular*⁹²—Within the synovial cavity of a joint

*Kellgren-Lawrence (KL) grading scheme*⁶⁷—Currently the most widely used and accepted standard for diagnosis of radiographic OA.

A KL grade of 0 indicates that no radiographic features of OA are present, while a KL grade of 1 is defined as doubtful joint space narrowing (JSN) and possible osteophytic lipping. Radiographic OA receives a KL grade of 2, denoting the presence of definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph. Further disease progression is graded as KL 3, characterized by multiple osteophytes, definite JSN, sclerosis, possible bony deformity, and KL grade 4, which is defined by large osteophytes, marked JSN, severe sclerosis, and definite bony deformity.

*Meniscus*⁸²—A soft-tissue structure that lines some joints and provides load distribution, shock absorption, and lubrication

*Multimodal treatment*⁹³—Therapy that combines more than one method of treatment. Also called combination therapy and multimodality therapy.

*Narcotic*⁹⁴—Opium and coca leaves and the several alkaloids derived therefrom; the best known of these alkaloids being morphia (morphine), heroin, and codeine, obtained from opium, and cocaine derived from the coca plant; all compounds, salts, preparations, or other derivatives obtained either from the raw material or from the various alkaloids; Indian hemp and its various derivatives, compounds, and preparations, and peyote in its various forms; isonipecaine and its derivatives, compounds, salts, and preparations; opiates.

*Neutraceutical*⁹⁵—A product isolated or purified from foods, generally sold in medicinal forms not usually associated with food, and demonstrated to have a physiological benefit or provide protection against chronic disease

*Nonsteroidal anti-inflammatory drug*⁸²—A broad group of chemically heterogeneous drugs that share important clinical and tissue effects: all have some analgesic, antipyretic, and anti-inflammatory activity. Includes aspirin, ibuprofen, indomethacin, naproxen, and others.

*Osteoarthritis*⁸⁸—Arthritis characterized by erosion of articular cartilage, either primary or secondary to trauma or other conditions, that becomes soft, frayed, and thinned with eburation of subchondral bone and outgrowths of marginal osteophytes

*Osteoarthritis of the knee*⁹⁶—Occurrence of osteoarthritis in the knee. Osteoarthritis of the knee is categorized clinically by the Visual Analog Scale (VAS) for pain. For pain intensity, the scale is most commonly anchored by “no pain” (score of 0) and “pain as bad as it could be” or “worst imaginable pain” (score of 100 [100-mm scale]).

No pain: 0-4 mm

Mild pain: 5-44mm

(continued)

Appendix E (continued)

Moderate pain: 45-74 mm

Severe pain: 75-100 mm

*Placebo*⁹⁷—A substance that does not contain active ingredients and is made to be physically indistinguishable (i.e., it looks and tastes identical) from the actual drug being studied

*Platelet-rich plasma*⁸²—Plasma with many more platelets than what is typically found in blood. The concentration of platelets—and, thereby, the concentration of growth factors—can be 5 to 10 times greater (or richer) than usual.

*Radiographs (x-rays)*⁹⁸—A noninvasive medical test that helps physicians diagnose and treat medical conditions. Imaging with x-rays involves exposing a part of the body to a small dose of ionizing radiation to produce pictures of the inside of the body.

*Steroids*⁸⁸—Large family of chemical substances, comprising many hormones, body constituents, and drugs, each containing the tetracyclic cyclopenta[*a*]phenanthrene skeleton

*Synovial fluid*⁸²—A fluid that has a very low coefficient of friction and provides lubrication and nutrients for joint chondrocytes; the straw-colored fluid in the joint that is formed by filtration of capillary plasma

*Synovitis*⁸²—A condition characterized by inflammation of the synovial lining

*Total knee arthroplasty or total knee replacement*⁹⁹—Surgical procedure in which damaged bone and cartilage is cut away from the thighbone, shinbone, and kneecap and replaced with an artificial joint made of metal alloys, high-grade plastics, and polymers

*Total joint arthroplasty or total joint replacement*⁸⁸—Surgical procedure in which parts of an arthritic or damaged joint are removed and replaced with a metal, plastic, or ceramic device called a prosthesis. The prosthesis is designed to replicate the movement of a normal, healthy joint.

*Viscoelastic*⁸²—Having mechanical properties dependent on the loading rate of an applied force

*Viscosupplements*⁸²—Intra-articular hyaluronic acid preparations commonly used to treat osteoarthritis; thought to increase joint lubrication

*Washout period*¹⁰⁰—A period in a trial during which the effect of a treatment given previously is believed to disappear

Acknowledgments and Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Collectively, all contributors received financial support from the Advanced Medical Technology Association to conduct the work required to produce this article.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Roy Altman: Consultant for Oletec, Ferring, Teva, and SST Corporation. Dr. Jeffrey Rosen: Member of Ferring Pharmaceuticals' Scientific Advisory Board. Dr. Vijay Vad: Owner of Vad Scientific, LLC and Vad Biolabs, LLC.

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