Consequences on Private Insurance Coverage
The AAOS Clinical Practice Guidelines and Hyaluronic Acid Injections

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Bedard et al. recently published a review on the impact of the 2013 American Academy of Orthopaedic Surgeons (AAOS) Clinical Practice Guideline (CPG) on intra-articular (IA) hyaluronic acid (HA) injections, also referred to as viscosupplementation, and concluded that there were subtle but important changes in the use of IA HA following the publication of the AAOS CPG and that these changes were warranted because of the high cost of the injections, given their questionable efficacy. However, we believe that consideration of the additional data supports a different conclusion and that the CPG has had a more detrimental impact on patient care. We submit that continued endorsement of this guideline may not be in the best interest of patients or the health-care system. Accordingly, we believe that the 2013 AAOS CPG should be reconsidered and modified to include a more comprehensive and perhaps more objective treatise on the guidelines for the nonsurgical treatment of knee pain due to osteoarthritis (OA).

The Impact
In 2016, the total population of the United States was 320,372,000; an estimated 292,320,000 citizens were covered by some form of health insurance. Of these, approximately 216 million citizens were covered by private insurance (Table I), of whom 178 million were covered through employer-based insurance. While Medicare, accounting for 53.4 million lives, covers all approved uses of IA HA injections, 17 major insurance carriers (including the largest, Anthem Blue Cross and Blue Shield) that account for nearly 64 million lives (29.6% of all private insurance-covered lives) do not pay for IA HA injections (Table II), citing the 2013 AAOS CPG as a primary reason. This decision of noncoverage means that patients pay, at a minimum, an estimated $1,600 for a course of 3 injections of Synvisc (Genzyme Biosurgery) (based on the average wholesale price of IA HA products, including $62.16 as the cost of administration per injection plus a Level-1 of first visit only of $90 [approximately $1,400 for Synvisc-One]) compared with an estimated $320 in copayment (assuming an average 20% copayment using Medicare fee-for-service as a standard) under insurance coverage.

The AAOS CPG and coverage decisions do not acknowledge the recently reported economic and medical benefits associated with viscosupplementation (IA HA) use, including (1) delayed time to knee replacement, (2) reduced pain medication usage (corticosteroids, nonsteroidal anti-inflammatory drugs [NSAIDs], and opioids), (3) better cost-effectiveness compared Covered through employer-based insurance.

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with standard-of-care treatments, (4) improved function, and (5) a favorable safety profile.

The Evidence

The 2013 AAOS CPG was based on a meta-analysis of published HA clinical studies that met the CPG and systematic review working group inclusion criteria. The guideline concluded that HA injections demonstrated significant differences in pain relief compared with saline solution injections. However, we believe that the AAOS CPG remains debatable since its evidence synthesis rules allowed only for the inclusion of Level-I evidence (randomized clinical trials) and not Level-III and Level-IV published evidence. This may deprive patients of access to additional treatment modalities, and the subjective inclusion criteria (such as age, Kellgren–Lawrence grade, primary outcome measures, activity level, comorbidities, etc.) that are used for patient selection in randomized clinical trials have been shown to substantially affect research outcomes. Additionally, the final negative recommendation ("We cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee"); strength of recommendation: strong) was based on the conclusion that the effect size was not "clinically significant," which the AAOS defined as "a statistically significant difference in treatment effect where the lower limit of the 95% confidence interval is greater than the minimal clinically important improvement" (MCID; MCII values were based on the published literature). This conclusion may have been based on flawed methodology and interpretation of minimal clinically important differences (MCIDs) of patient-reported outcomes. At present, there is no universal standard for calculating MCIDs (we are aware of as many as 9 published methods), especially when comparing population-based studies with individual-based studies, which has led to often disparate methodological and/or interpretation problems. Although there is value in understanding the MCID for assessing clinical appropriateness, it is only one of many important clinical tools (such as patient-reported outcome instruments, clinical experience, clinical study designs, demographics and patient variability, comorbidities, physical functional state, quality of life [both psychological and social aspects], tolerability, convenience, availability, physician’s preference and experience, cost, alternative treatment options, etc.) for evaluating treatment safety and effectiveness. At this point, basing the effectiveness of an intervention solely on such an evaluation may be considered shortsighted. Furthermore, meta-analysis examining the HA class may incorporate additional levels of bias. These biases may include (1) regulatory bias, resulting from inclusion of studies from nonapproved U.S. products; (2) historical bias, resulting from comparison of studies over decades; (3) effectiveness bias, resulting from exclusion of studies not using the currently accepted or adopted outcome measures or methodology; and (4) control bias, resulting from failure to distinguish between true placebo controls and active comparators (Table III). The issue of control bias is especially important when examining the comparative effect size of IA HA injections, given the recent reports of the clinical effectiveness of IA saline solution injections, which are typically used as control comparators (including arthrocentesis and the use of up to 4 g/day of acetaminophen) in HA studies. The use of IA saline solution as a control comparator can diminish the net effect size of an IA HA intervention because the comparator is an active clinical intervention.

### TABLE I Summary of the U.S. Population Health-Care Coverage*

| Source of Population | No. of Lives | U.S. Population |
|----------------------|--------------|-----------------|
| Total U.S. population | 320,372,000  | 100.0%          |
| Uncovered by health insurance | 28,052,000  | 8.8%            |
| Covered by health insurance | 292,320,000 | 91.2%           |
| Medicare-covered lives | 53,372,000  | 16.7%           |
| Medicaid-covered lives | 62,303,000  | 19.4%           |
| Private insurance-covered lives | 216,203,000 | 67.5%           |

*Medicare and Medicaid-covered lives include the elderly and citizens with disabilities who qualify for dual coverage.

### TABLE II Summary of the U.S. Health-Care-Covered Lives and Noncoverage of IA HA Injections

| Major Insurance Plans Not Covering IA HA Injections∗ | Covered Lives | Privately Insured U.S. Lives | Total U.S. Lives |
|------------------------------------------------------|---------------|------------------------------|------------------|
| Total private health insurance-covered lives         | 216,203,000   | 100.0%                       | 67.5%            |
| BCBS (non-coverage)                                  | 46,574,621    | 21.5%                        | 14.5%            |
| Kaiser Health Plan U.S.                              | 9,185,680     | 4.2%                         | 2.9%             |
| Medicaid (NY, NC, OK)                                | 8,137,430     | 3.8%                         | 2.5%             |
| Total private health insurance not covering IA HA injections | 63,897,731 | 29.6%                       | 19.9%            |

*Published coverage policies: Anthem Blue Cross and Blue Shield (BCBS); Kaiser Health Plan U.S.; New York Medicaid; North Carolina Medicaid; Oklahoma Medicaid; BCBS of California, Florida, Massachusetts, Kansas City and Kansas, New York (Health Now), Arkansas, and Rhode Island; Regence Blue Cross; Premera BCBS; Group Health Coop; and Lifewise Health Plan of Washington. †The BCBS association is a federation of 36 separate U.S. health insurance organizations and companies providing health insurance to >100 million lives. The plans denying coverage, primarily Anthem Blue Cross and Blue Shield (BCBS), have a dominating or partial market presence in the states of AK, CA, CO, CT, FL, GA, ID, IN, KS, KY, MA, ME, MO, NH, NV, NY, RI, OH, VA, WA, and WI.
TABLE III Types of Bias

| No. | Bias           | Description                                                                 |
|-----|----------------|-----------------------------------------------------------------------------|
| 1   | Regulatory     | Resulting from the inclusion of clinical studies of nonapproved U.S. products (products not approved may provide a negative bias) |
| 2   | Historical     | Resulting from the comparison of clinical trials over decades, which may have led to the exclusion of studies not meeting current practices and thereby may not include studies of the first approved products |
| 3   | Effectiveness  | Resulting from the exclusion of studies utilizing validated outcome measures at the time of design but not using the currently accepted or adopted outcome measures or methodology (excludes earlier studies) |
| 4   | Control        | Resulting from the failure to distinguish true placebo controls from active comparators (saline solution injections) |

(arthrocentesis, saline solution injection of diluting pain mediators, and access to up to 4 g/day of acetaminophen) instead of a true placebo (control bias). Reliance on a single outcome measure also has been challenged, with a combination of patient-reported outcomes and responder analysis being proposed as a more appropriate standard for outcome assessment.

We believe that the AAOS workgroup, in their CPG review, potentially applied a somewhat flawed methodology to make a strong recommendation against the use of IA HA, given that all of the evidence that we believe to be relevant should have been considered further. These selection biases can be easily tested, and we recommend stratifying these variables. The CPG concluded that the benefits were exceeded by the potential harm and/or the quality of the supporting evidence for this recommendation is high. However, results from clinical studies and postmarketing reports have demonstrated that IA HA injections are not harmful. The adverse reactions that the CPG cite also are limited and seem to be restricted to a single product, which may be related to the chemical cross-linking manufacturing process. Accordingly, we question the basis of the "strong" recommendation against the use of IA HA injections.

In contrast, 2 of what we believe are the most comprehensive and perhaps least biased meta-analyses of HA effectiveness (based on affiliation or sponsorship: research sponsored by the Cochrane Collaboration and the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services) concluded that IA HA injections were statistically superior to IA saline solution injections, with a clinically meaningful difference. Using a network meta-analysis, Bannuru et al. showed that IA HA injections have a clinical effect size that is 2 to 3 times greater than that of standard-of-care oral pain medications (Table IV). More importantly, Bannuru et al. and Altman et al. have shown that IA saline solution injections (a standard control comparator to IA HA injections in clinical trials) are not placebos but are active comparators (Table V) as their effect size is comparable with standard-of-care NSAIDs. Therefore, using IA saline solution as a placebo comparator could dilute and diminish the effect size that is observed with IA HA injections (control bias).

The Osteoarthritis Research Society International (OARSI) guidelines for the nonsurgical management of knee OA concluded that IA HA injections had an estimated effect size (standardized mean difference) of 0.37 to 0.46 for pain, based on "good quality of evidence," which equaled or exceeded the effect size for NSAIDs. However, based on some inconsistent conclusions among the meta-analyses and conflicting results regarding the safety of some IA HA products, the panel voted to recommend IA HA injections with an "uncertain" designation for knee-only OA and as "not appropriate" for multiple-joint OA. In a 2011 meta-analysis that was included in the OARSI guidelines, IA HA demonstrated a small but statistically significant reduction in OA knee pain by week 4, with a peak at week 8 (reaching moderate clinical significance) and residual benefit until 24 weeks.

Another meta-analysis from 2012 found moderate benefits of IA HA for pain and physical function in knee OA, although sensitivity analyses, including analysis of only larger studies with adequate blinding, found only a small effect size for pain. The differences in the conclusions between the 2011 and 2012 analyses could have been due to the exclusion of studies with a smaller sample size and the use of different outcome measures.

TABLE IV Intra-Articular HA Clinical Effect Size Versus Other Treatments for OA Knee Pain*

| Comparator       | Placebo | APAP | IA Saline Solution† | Celebrex | Naproxen | Ibuprofen | Diclofenac | IA Steroids |
|------------------|---------|------|---------------------|----------|----------|-----------|-----------|-------------|
| IA HA            | 0.63    | 0.45 | 0.34                | 0.30     | 0.25     | 0.19      | 0.11      | 0.02        |

*HA = hyaluronic acid, OA = osteoarthritis, APAP = acetaminophen, and IA = intra-articular. †IA saline solution control = arthrocentesis, dilution with saline solution injection, and prn (as needed) APAP. Adapted, with permission, from: Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med. 2015 Jan 6;162(1):46-54.
sample size and the inclusion of an additional 5 unpublished studies that reported nonsuperiority of HA compared with placebo in the 2012 meta-analysis. Furthermore, systematic reviews published after the AAOS and OARSI guidelines had been issued also have drawn inconsistent conclusions regarding the clinical utility of HA injections. A meta-analysis of double-blinded sham-controlled studies found no clinically important improvement in pain or other outcomes with HA treatment versus placebo. In contrast, a 2018 systematic review showed “strong evidence” for clinically important treatment effects for knee OA when using IA HA formulations with a molecular mass between 1,500 kDa and >6,000 kDa compared with nonoperative treatments. In the recent OARSI guidelines, IA HA was conditionally recommended in individuals with knee OA in all groups. Furthermore, it was noted that IA HA may have beneficial effects on pain at week 12 of treatment and beyond, as well as a more favorable long-term safety profile compared with repeated IA corticosteroids. Notably, the American Medical Society for Sports Medicine (AMSSM) recommended the use of HA for appropriate patients with knee OA based on the number of participants meeting the Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) criteria, which are different and might be considered more relevant than methods used in the earlier AAOS CPG. The continued contradictory recommendations from meta-analyses, together with a lack of treatment consensus among clinicians, underscore the need for well-designed, prospective, large population-based studies (pragmatic studies) to evaluate the real-world effectiveness of IA HA for knee OA and inform decision-makers regarding the comparative balance of benefits, burdens, and risks of IA HA.

The Clinical Options
The value (clinical benefit) and associated risk (safety) of IA HA in controlling OA knee pain should be compared with those of other nonsurgical treatments. Guidelines generally recommend exercise, weight loss, and physical therapy, followed by simple analgesics, NSAIDs, or other analgesics. While some studies have shown these treatments to be cost-effective, advocating the use of nonsurgical management plans for knee OA in the absence of workable blueprints and practical means of implementation of a clear and well-substantiated consensus on treatment algorithms will render most nonsurgical plans for knee OA ineffective in real-world situations.

**Oral Pain Medications**
Although acetaminophen is often the first oral pain medication that is recommended in treatment algorithms for OA knee pain, recent studies have concluded that there is no role for single-agent acetaminophen for the treatment of patients with chronic OA pain, irrespective of dose. In addition, the potential toxicity associated with acetaminophen has further called into question its use based on this associated risk (potential safety profile).

Although NSAIDs are used as standard nonsurgical treatment of chronic OA knee pain, while effective, safety issues associated with NSAIDs need to be carefully considered, especially since patients with knee OA often have comorbidities that can exacerbate these adverse effects.

**Due to safety concerns**, in 2005, the U.S. Food and Drug Administration (FDA) also required all NSAID (including cyclooxygenase-2 [COX-2]-selective inhibitor) manufacturers to include “black box” warnings highlighting the potential for increased risk of cardiovascular events and serious gastrointestinal bleeding. Solomon et al. examined all-cause mortality for Medicare beneficiaries with a diagnosis of rheumatoid arthritis or OA who were receiving a nonselective NSAID or a selective COX-2 inhibitor. The estimated all-cause mortality incidence rate was 48/1,000 person-years for nonselective NSAIDs and 47/1,000 person-years for selective COX-2 inhibitors. Furthermore, based on conservative calculations, at least 16,500 NSAID-related deaths occur per year in arthritis patients. In contrast, there have been no reported product-associated deaths with HA injections.

The concerns regarding opioid use for chronic pain management are well-documented and irrefutable and they are not a viable option in the treatment paradigm. Solomon et al. noted that the all-cause mortality, primarily from overdosing with opioids, for Medicare beneficiaries was 75/1,000 person-years. Using the same assumptions as above, this could translate to almost 80,000 deaths annually. An epidemiologic study presented at the American Academy of Addiction Psychiatry 23rd Annual Meeting and Scientific Symposium reported that approximately 20% of individuals who are ≥65 years old take analgesics several times per week and the rate of abuse or addiction in those with chronic pain is 18%. Data from the Substance Abuse and Mental Health Services Administration indicated that 2.8 million elderly patients in the U.S. abused prescription drugs in 2012, which is expected to increase to >4.4 million by 2020.

**Other Local Therapies**
IA injections can deliver therapy locally if the symptoms of OA are isolated, which is particularly desirable when comorbidities

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### TABLE V Placebo Pill, IA Saline Solution, and Oral NSAID Effect Size for Treatment of Knee OA *

| Comparator       | APAP  | IA Saline Solution | Celebrex | Naproxen |
|------------------|-------|--------------------|----------|----------|
| Placebo pill     | 0.18  | 0.29               | 0.33     | 0.38     |
| APAP             | 0.11  | 0.15               | 0.20     |          |
| IA saline solution† | 0.04  | 0.09               |          |          |
| Celebrex         |       | 0.05               |          |          |

*IA = intra-articular, NSAID = nonsteroidal anti-inflammatory drug, OA = osteoarthritis, and APAP = acetaminophen. †IA saline solution control = arthrocentesis, dilution with saline solution injection, and pm (as needed) APAP. Adapted, with permission, from: Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med. 2015 Jan 6;162(1):46-54.
and drug-drug interactions are of particular concern in certain patient populations. IA corticosteroid injections are perhaps the most common treatment option for OA knee pain, and recent reviews have demonstrated moderate efficacy over 1 to 2 weeks and small-to-moderate efficacy over 4 to 6 weeks after the end of treatment. While in vitro studies have demonstrated deleterious effects of corticosteroids on cartilage, there is little clinical evidence that repeat corticosteroid injections every 3 months alter the progression of OA. This notion has recently been refuted in a review by Kompel et al., in which they summarized the clinical data supporting the adverse joint events after IA corticosteroid injections. Other IA injections, such as platelet-rich plasma (PRP) and cell-based therapies, show some promise in the treatment of OA knee pain but are awaiting large well-controlled clinical studies.

Despite some positive results in early published clinical studies, the complexity and inherent variability in the preparation of PRP, as well as cell-based therapy preparations, suitable control comparators, well-defined sourcing of cells, and appropriate delivery systems, have meant that definitive conclusions are difficult to make with respect to the general adoption of these therapies into the nonsurgical treatment paradigm. Furthermore, since none of these therapies are approved by the FDA (only the instruments used in their preparation are FDA-“cleared” as Class-II medical devices by a 510[k] process) and are therefore not reimbursed, the out-of-pocket costs can be prohibitive to patients and further limit their widespread adoption. Despite the fact that the evidence supporting the use of PRP, stem cells, and other injections for the management of OA knee pain is conflicting, the AAOS nonetheless provided an “inconclusive” recommendation regarding their use in contrast to IA HA. We believe that a substantial body of evidence, as outlined in this paper, suggests that IA HA injections can be a valuable treatment option to the clinician in the management of OA knee pain.

**Clinical Selection**

Several international expert groups have provided recommendations for the use of IA HA in specific patient populations. For example, a workgroup of clinical experts developed appropriate use criteria to identify the types of patients for whom HA use is appropriate. This group determined that the use of HA injections in OA knee treatment is appropriate for patients with confirmed mild or moderate knee OA who have not received other therapies, or for those who have been unsuccessful with or have had an incomplete response to other nonpharmacologic or pharmacologic therapies for the knee. The group also concluded that HA injections are contraindicated in patients with a local skin infection at the injection site and/or an active joint infection. This clinical selection is similar to that observed in other conditions, such as with vertebroplasty, in which a rigorous selection of patients is of utmost importance, and with epidural steroid injections for patients with lumbar spinal stenosis, where there is limited evidence to support their long-term benefit.

The technique of injection is of importance for efficacy and tolerance, with the lateral-patellar approach being preferable. In contrast to palpation-guided anatomical injections, ultrasound-guided knee injections have been shown to have improved injection accuracy, resulting in improved patient-reported outcomes and cost-effectiveness.

**Summary**

We believe that eliminating the use of IA HA as one of the nonsurgical treatment options available to clinicians would not be judicious. While there may be some debate on the efficacy of HA injections, several meta-analyses and systematic reviews support their use, with minimal safety concerns, and numerous studies have offered reasonable and scientifically valid explanations to clarify the discrepancies in conclusions from various reports. What is not in question is the safety profile of the product class, particularly in the targeted patient population, along with the lack of product-drug interactions. In addition, there is no issue with patient compliance or overuse as there is with oral pain medications.

We believe that a more judicious approach to appropriate OA treatment would be to adopt the more recent recommendations to optimize the outcomes of IA HA with better patient selection and earlier treatment. Furthermore, we believe that restricting the availability of a safe and effective treatment option such as HA clearly does not help our patients, limits our treatment repertoire as clinicians, and therefore warrants the reevaluation of the AAOS CPG on IA HA treatment.

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