



**Washington State
Health Care Authority**

Health Technology Assessment Program

**Health Technology Clinical Committee
Hyaluronic Acid/ Viscosupplementation**

Osteoarthritis Background

- OA affects around 27 million people (US); progressive and no cure
 - OA of the knee may affect 37% of the over 60 year old population
- Management options:
 - Lifestyle changes: Physical therapy and exercise; systemic and topical analgesics; bracing/orthotics; corticosteroid and ACS injections; alternative and complimentary therapy; surgical joint replacement
- OA Knee problems may involve a decreased level of synovial fluid in the joint, as well as loss of cartilage and inflammation.

HA Injection – Technology Description

Varying HA types/treatment strategies

- ❑ Cross-linked derivative vs natural; Different molecular weights
- ❑ 1 to 3 to 5 injections per course of treatment

Unknown mechanism of action for HA

- ❑ Hyaluronic acid is a natural component of synovial fluid and lubricates joints/provides shock absorption; which may decrease with OA
- ❑ HA passes through joints cyclically, with residence in joint typically not more than hours to days.
 - Replacement HA thus not thought to be mechanical lubricant or shock absorber

FDA approval status

Intra-articular injection of HA categorized as a biologic device, first FDA approval 1997

- Treatment of pain associated with Knee OA
- patients who have not responded adequately to conservative non-pharmacologic therapy (physical therapy)
Or simple analgesics (acetaminophen)

Contraindications:

- known allergy to hyaluronate preparations, or to birds or bird products
- infections or skin diseases at the injection site or knee joint

Off Label: reports of use in hip, ankle, shoulder and other joints; retreatment

<http://www.pbm.va.gov>

- ❑ **Technology dissemination**
 - Rapid uptake in past several years, especially newer products; escalating utilization
- ❑ **Potential Benefits**
 - Pain relief and functional improvement
- ❑ **Potential Drawbacks**
 - Treatment is additive
 - Uncertain benefit and duration
 - Injection related harms
 - Cost

<u>Primary Criteria</u>	
Potential patient harm/safety concerns:	Low
Concerns about therapeutic efficacy or diagnostic accuracy and appropriateness of outcomes for patients:	Med
Estimated total direct cost per year (estimated increase/decrease):	High
<u>Secondary Criteria</u>	
Number of persons affected per year:	High
Severity of condition treated by technology:	Med
Policy related urgency/diffusion concern:	High
Potential or observed variation:	High
Special populations/ethical concerns:	Low

Tech Project Overview

- **Key Questions** (January 2010)
 - Joint Clinical effectiveness; product variation; adverse effects; cost implications
- **Report** (March-April 2010)
 - OHSU MED project – collaborative topic
 - Large evidence base with previous systematic review, focus on summarizing and update
 - Public comment: 5 providers; 3 industry; 1 agency
- **Clinical Expert** (Mar-April 2010)
 - Contact to WSMA; WSOA; Committee; Vendor
 - Follow up six referrals; no response or unavailable

- **No Medicare National Coverage Decision**
- Six Guidelines – All cite evidence, Rating: 3 Good and 3 Poor

Recommending Body, Year Published	Outcome	Overall Quality
ACR 2000	Intraarticular hyaluronan therapy is indicated	Y - Poor
APS 2002	Injection of HA supplements into the knee may be considered in persons with OA	Y- Poor
AAOS 2008	AAOS concluded that they could not recommend for or against as evidence is inconclusive	Y - Good
NICE 2008	Intraarticular hyaluronan injections are not recommended for the treatment of OA of the knee, or any other joint.	Y - Good
VA 2008	Evidence supports the use of intraarticular hyaluronan or hylan injections for OA of the knee.	Y - Poor
Zhang 2008 (OARSI)	Injections of intraarticular hyaluronate may be useful in patients with knee OA	Y - Good

Hyaluronic Acid/ Viscosupplementation

Questions

Washington State HTA Viscosupplementation

May 14, 2010



never stop moving™

WA State Health Plans that Cover Viscosupplementation

- Aetna
- Premera Blue Cross
- Regence Blue Shield
- PacifiCare
- Secure Horizons
- Noridian Administrative Services (Medicare Carrier)
- Washington State Department of Labor & Industries

WA State Health Plans that cover Viscosupplementation

Aetna

- The member has documented symptomatic osteoarthritis of the knee; *and*
- The member reports pain which interferes with functional activities (e.g., ambulation, prolonged standing); *and*
- Conservative therapy (including physical therapy, pharmacotherapy (e.g., non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen (up to 1 g four times per day) and/or topical capsaicin cream)) has been attempted in each joint to be treated with viscosupplements and has not resulted in functional improvement after at least 3 months or the member is unable to tolerate conservative therapy because of adverse side effects; *and*
- The member has failed to adequately respond to aspiration and injection of intra-articular steroids; *and*
- The pain cannot be attributed to other forms of joint disease; *and*
- There are no contraindications to the injections (e.g., active joint infection, bleeding disorder).

Premera Blue Cross

- Appropriate candidates for hyaluronan injections are those who have failed conservative therapy with NSAIDs or who have contraindications to NSAID therapy.

Regence Blue Shield

- No published policy

WA State Health Plans that cover Viscosupplementation

PacifiCare

- No published policy

Secure Horizons

- No published policy

Noridian Administrative Services (Medicare Carrier)

- No published policy

Washington State Department of Labor & Industries

Patient has failed to benefit from or is unable to tolerate **all of the following** therapies recommended by the American College of Rheumatology:

- Non-pharmacological therapies (e.g., physical therapy),
- Non-opioid analgesics (e.g., acetaminophen) and
- Treatment with non-steroidal anti-inflammatory drugs (NSAIDs). Intolerance and therapeutic failure must be documented with at least a 1 week trial of 2 formulary products from different

COCHRANE SUMMARY

Viscosupplementation for the treatment of osteoarthritis of the knee

Osteoarthritis (OA) is the most common form of chronic arthritis worldwide. Hyaluronan and hylan (HA) products provide opportunity to treat OA in individual knee joints. To evaluate the efficacy, effectiveness and safety of HA products, in knee OA, we have conducted a systematic review using Cochrane methodology. The analyses support the contention that the HA class of products is superior to placebo. There is considerable between-product, between-variable and time-dependent variability in the clinical response. The clinical effect for some products against placebo on some variables at some time points is in the moderate to large effect size range. In general, sample size restrictions preclude any definitive comment on the safety of the HA class of products, however, within the constraints of the trial designs employed, no major safety issues were detected. The analyses suggest that viscosupplements are comparable in efficacy to systemic forms of active intervention, with more local reactions but fewer systemic adverse events, and that HA products have more prolonged effects than IA corticosteroids.

Overall, the aforementioned analyses support the use of the HA class of products in the treatment of knee OA.

Medicare Current Reimbursement for Viscosupplementation

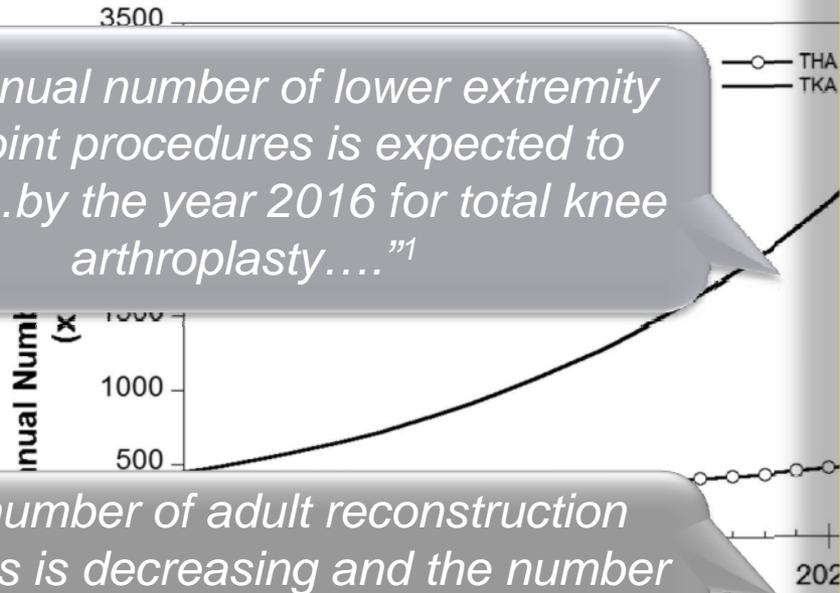
Product	# of injections for 26 weeks of relief	Medicare Reimbursement 2 nd Q2010	Total injection costs	Administrati on cost @74.00	Total Treatment Costs
Hyalgan/ Supartz	5	\$91.95	\$459.75	\$370	\$829.75
Orthovisc	3	\$176.70	\$530.10	\$222	\$752.10
Synvisc	3	\$188.48	\$565.44	\$222	\$787.44
	# of injections for 12 weeks of relief				
Euflexxa	3	\$113.79	\$341.37	\$222	\$563.37

Vinod Dasa, MD

TKA Procedures Expected to Increase

“The annual number of lower extremity total joint procedures is expected to double...by the year 2016 for total knee arthroplasty....”¹

“The number of adult reconstruction surgeons is decreasing and the number of primary and revision TJA procedures is increasing.”¹



ORTHOPEDIC SURGEON WORKFORCE AND VOLUME ASSESSMENT FOR TOTAL HIP AND KNEE ARTHROPLASTY IN THE UNITED STATES—PREPARING FOR AN EPIDEMIC

Richard Iorio, MD*, William J. Robb, MD*, William L. Healy, MD*, Daniel J. Berry, MD*, William J. Hozack, MD*, Richard F. Kyle, MD*, David G. Lewallen, MD*, Robert T. Trousdale, MD, William A. Jiranek, MD, Van P. Stamos, MD, Brian S. Parsley, MD*

Introduction: The annual number of lower extremity total joint procedures is expected to double by the year 2026 for total hip arthroplasty (THA) and by 2016 for total knee arthroplasty (TKA), reaching 572,000 primary THA and 3.48 million primary TKA by 2030. The annual number of revision THA (97,000 by 2030 [137% increase]) and revision TKA (268,000 by 2030 [601% increase]) are also increasing drastically. The average hospital Medicare payment for DRGs 209 and 544 increased 24% between 1991 and 2007. The average physician payment for total joint arthroplasty (TJA) declined 39% in the same interval.

Methods: A survey of the membership of the American Academy of Orthopaedic Surgeons and Adult Reconstruction Fellowship programs was undertaken to assess the surgical workforce needed for the expected drastic increase in primary and revision TJA procedures.

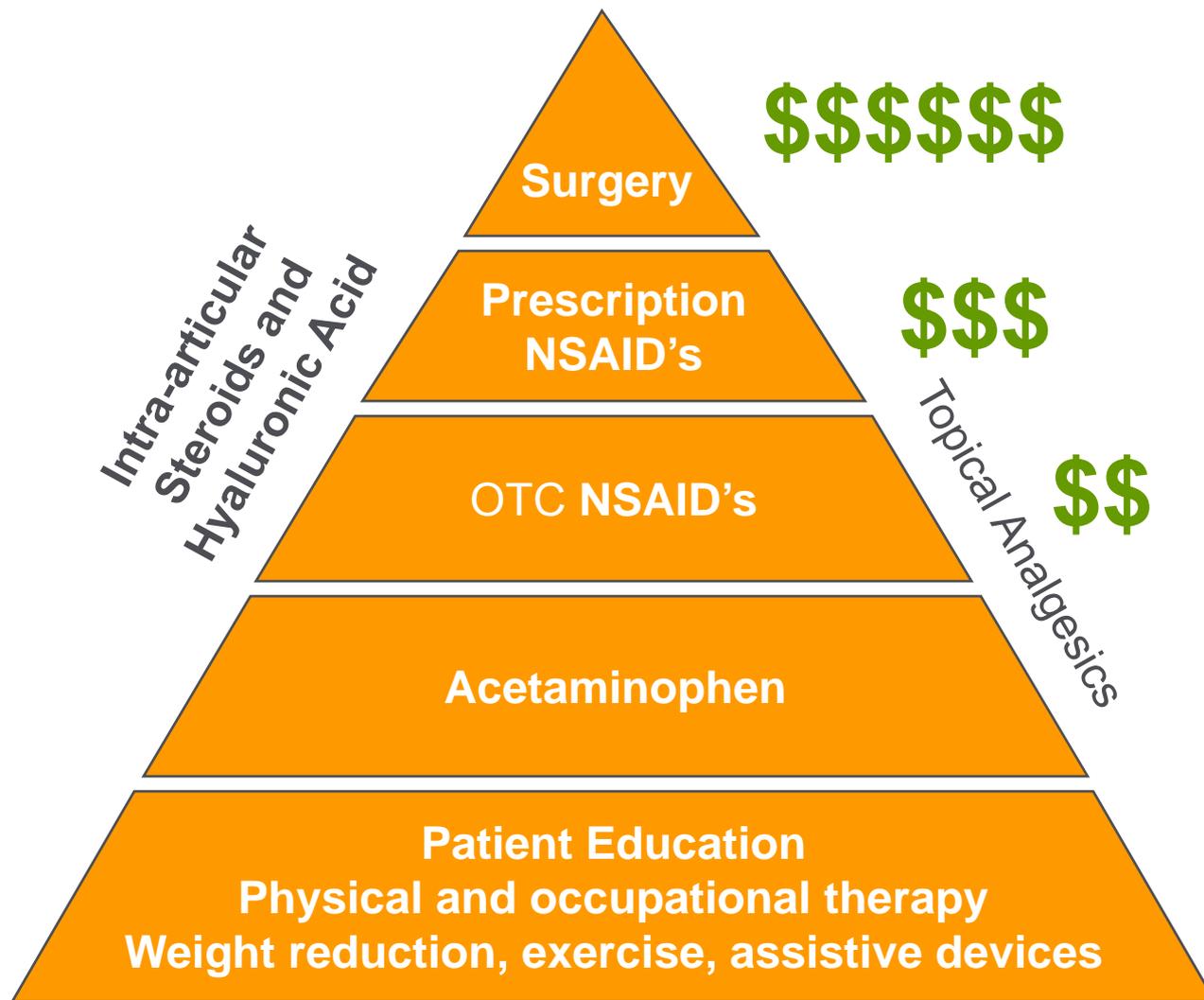
Results: In 2005, 7% of AAOS members identified themselves as primary surgical specialists for adult hip and knee. More than 90% of 620 graduating residents enrolled in a fellowship. For 2007 to 2008, 64 US adult reconstruction fellowship programs are recruiting active fellows. Ten programs have been discontinued over the past 5 years. For 2006 to 2007, there were 62 programs with 119 fellowship positions. For 2006 to 2007, 92 (77.3%) of 119 fellowships were filled. For 2007 to 2008, 74 (61.67%) of 120 fellowships were filled. For 2006 to 2007, 18 (19.6%) of 92 fellows were international medical graduates. For 2007 to 2008, 20 (27%) of 74 fellows were international medical graduates.

Conclusion: The number of adult reconstruction surgeons is decreasing and the number of primary and revision TJA procedures is increasing. Decreasing reimbursement may be negatively affecting the development of adult reconstruction surgeons. A critical adult reconstruction surgical workforce shortage is predicted over the next 25 years.

- Projected number of primary total hip arthroplasty (THA) and total knee arthroplasty (TKA) procedures in the U.S. from 2005 to 2030¹

1. Kurtz S, Ong K, Lau E, et al. *J Bone Joint Surg.* 2007;89:780-785.

Widely Accepted Treatment Paradigm



Steroid Injections

Disadvantages:

Should not be used in diabetic patients: ↑ Blood glucose within first 24 hrs

Has been shown to be deleterious to cartilage and ligaments

In Vitro Cytotoxic Effects Of Benzalkonium Chloride In Corticosteroid Injection Suspension

Daniel Davis
Mathew Cyriac, Albany, NY
Dongxia Ge, MD, MS
Zongbing You, MD, New Orleans, LA
Felix H Savoie, III MD, New Orleans, LA

Lidocaine Potentiates the Chondrotoxicity of Methylprednisolone

Venkat Seshadri, M.D., Christian H. Coyle, Ph.D., and Constance R. Chu, M.D.

The effect of intra-articular injection of betamethasone acetate/betamethasone sodium phosphate on blood glucose levels in controlled diabetic patients with symptomatic osteoarthritis of the knee

George Habib · Ahmed Safia



Journal of Orthopaedic Research 19 (2001) 688-695

Journal of
Orthopaedic
Research
www.elsevier.nl/locate/orthres

Corticosteroids alter the differentiated phenotype of articular chondrocytes

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Received 18 January 2000; accepted 19 July 2000

Effects of Local Injection of Corticosteroids on the Healing of Ligaments

A FOLLOW-UP REPORT**†

BY MICHAEL E. WIGGINS, M.D.†, PAUL D. FADALE, M.D.‡, MICHAEL G. EHRLICH, M.D.‡,
AND WILLIAM R. WALSH, PH.D.†, PROVIDENCE, RHODE ISLAND

Investigation performed at the Biomechanics Laboratory, Department of Orthopaedics, and the Division of Engineering, Brown University School of Medicine, Rhode Island Hospital, Providence

Effect of Intra-Articular Corticosteroids on Ligament Properties

A Biomechanical and Histological Study in Rhesus Knees

FRANK R. NOYES, M.D.,* EDWARD S. GROOD, PH.D.,*
NOEL S. NUSSBAUM, PH.D.,** AND SHELDON M. COOPER, M.D.†

Corticosteroids: Efficacy Decline Over Time

Arthritis & Rheumatism (Arthritis Care & Research)
 Vol. 51, No. 12, December 15, 2009, pp 1704–1711
 DOI: 10.1002/art.24925
 © 2009, American College of Rheumatology

ORIGINAL ARTICLE

Therapeutic Trajectory of Hyaluronic Acid Versus Corticosteroids in the Treatment of Knee Osteoarthritis: A Systematic Review and Meta-Analysis

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 CHRISTOPHER H. SCHMID,¹ AND TIMOTHY E. McALINDON¹

Objective. To compare the efficacy of intraarticular hyaluronic acid with corticosteroids for knee osteoarthritis (OA).
Methods. Our data sources were Medline, EMBASE, CINAHL, BIOSIS, and the Cochrane database, as well as hand-searched reviews, manuscripts, and supplements. For unpublished data we used author contacts. Randomized trials that reported effects of intraarticular hyaluronic acid versus corticosteroids on knee OA were selected based on inclusion criteria. Two reviewers extracted data independently. Using a random-effects model, we computed effect sizes for pain change from baseline at 2, 4, 8, 12, and 26 weeks. We also performed multivariate analyses accounting for within and between-study covariance. We performed sensitivity analyses for trials that reported intent-to-treat (ITT) analysis and blinding, and directly compared Hyalga with methylprednisolone.
Results. The 7 eligible trials included 606 participants. Five reported ITT analyses. At week 2 the effect size was -0.29 (95% confidence interval [95% CI], -0.45 , -0.12) favoring corticosteroids; at week 4 it was -0.01 (95% CI -0.23 , 0.21) suggesting equal efficacy. At week 8 the effect size was 0.22 (95% CI -0.05 , 0.49) favoring hyaluronic acid, and at week 12 it was 0.25 (95% CI 0.02 , 0.48) favoring hyaluronic acid. At week 26 the effect size was 0.29 (95% CI 0.16 , 0.59), favoring hyaluronic acid. The multivariate analyses and sensitivity analyses generated consistent results.
Conclusion. From baseline to week 4, intraarticular corticosteroids appear to be relatively more effective for pain than intraarticular hyaluronic acid. By week 4, the 2 approaches have equal efficacy, but beyond week 8, hyaluronic acid has greater efficacy. Understanding this trend is useful to clinicians when treating knee OA.

INTRODUCTION

Knee osteoarthritis (OA) is a common and progressive joint disease. With an estimated incidence rate of 240 per 100,000 person-years (1), it is a major public health problem in the US and often results in early retirement and joint replacement. In the absence of effective disease-modifying medical interventions for knee OA, treatments are primarily symptomatic in nature, often including in-

traarticular injections of a corticosteroid or hyaluronic acid.

Corticosteroids have been employed for years in the treatment of OA, and as a result rheumatologists have substantial clinical experience of their utility and effectiveness. Consensus statements widely recommend corticosteroids as useful adjunctive treatment in the management of knee OA (2–4). Clinical trials and meta-analyses have demonstrated their efficacy (5). Hyaluronic acid, a large viscoelastic glycosaminoglycan that is naturally present in healthy joint fluid, is a relatively new intervention that is now widely used. It confers to joint fluid a number of protective properties, including shock absorption, traumatic energy dissipation, protective coating of the articular cartilage surfaces, and lubrication (6).

The original biologic rationale for the therapeutic use of synthetic hyaluronic acid in knee OA was its potential to increase the viscosity of synovial fluid (7). Therefore, the basis for the Food and Drug Administration's approval for hyaluronic acid was as a medical device rather than a pharmaceutical, and despite many placebo-controlled

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 Submitted for publication March 20, 2009; accepted in revised form August 10, 2009.

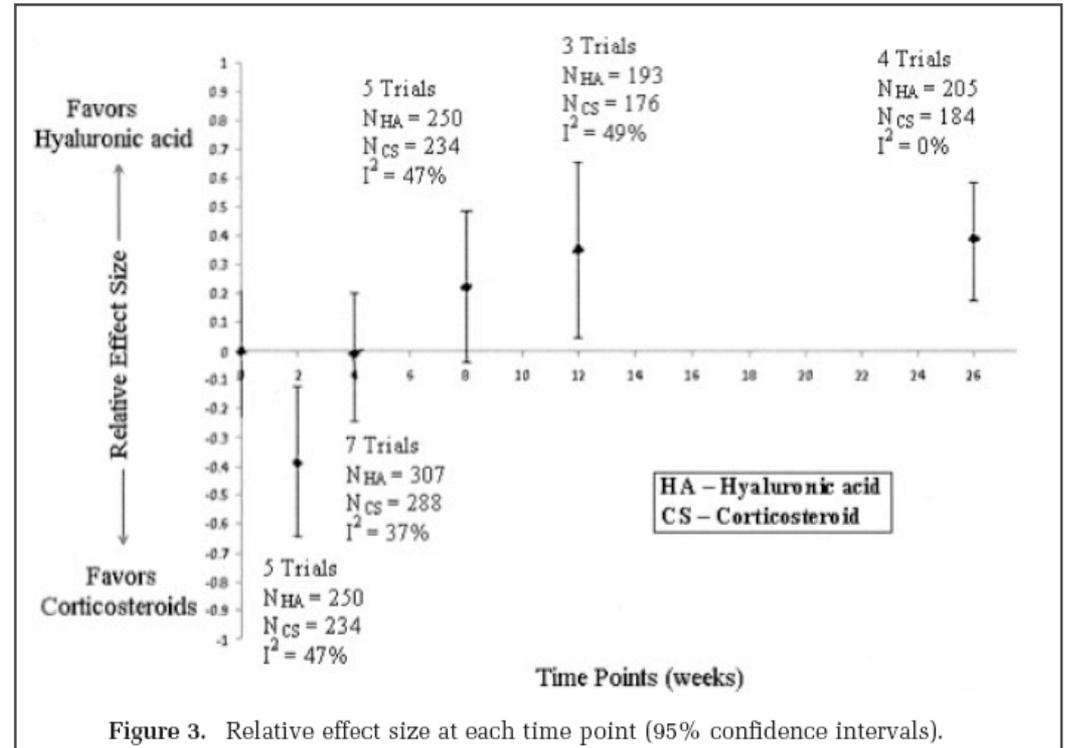


Figure 3. Relative effect size at each time point (95% confidence intervals).

IA-HA Science...

CLINICAL ORTHOPAEDICS AND RELATED RESEARCH
Number 466, pp. 241-248
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Hyaluronan Suppresses IL-1 β -induced Metalloproteinase Activity from Synovial Tissue

David D. Waddell, MD^{*}; Oleg V. Kolomytkin, PhD^{*}; Sharon Dunn, PhD[†]; and Andrew A. Marino, PhD^{*‡}

Fig 4A–B. (A) When synovial biopsy specimens from patients with advanced OA were cultured in the presence of IL-1 β (100 pg/mL) for 24 hours, the decrease in MMP activity in the supernatant resulting from the addition of HA (8 mg/mL) was not proportional to HA average molecular mass (HA_{av}) of 0.6, 2.3, and 1.2 MDa for Hyalgan[®], Orthovisc[®], and Supartz[®], respectively; C = control specimens (no IL-1 β). The results of five patients are shown in each of the three panels (three experiments). (B) Supartz[®] (1.2 MDa) and Synvisc[®] (12.8 MDa) (data from Fig 2A) were greater than 90% effective and Hyalgan[®] (0.6 MDa) and Orthovisc[®] (2.3 MDa) were approximately 20% effective in blocking IL-1 β -induced MMP activity. Bar and whiskers represent mean and standard deviation. * = $p < 0.05$ compared with IL-1 β (paired t test)

Degrading effect by advanced glycation end products and suppressing effect by hyaluronan in human meniscus cells from osteoarthritis knee

+Hiraiwa H; Sakai T; Mitsuyama H; Hamada T; Yamamoto R; Omachi T; Inukai N; Ohno Y; Nakashima M; Ishiguro N

Thus, we thought that HA could suppress AGE induced expression of MMP-1 and -3 via CD44 in meniscus cells from OA knee and suggested that HA could be effective for not only improvement of OA symptoms but also suppression of the progression of OA knee.

I. Pasquali Ronchetti, D. Guerra¹, F. Taparelli¹, F. Boraldi¹, G. Bergamini¹, G. Mori¹, F. Zizzi¹ and L. Frizziero¹

Department of Biomedical Sciences, University of Modena and Reggio Emilia, Modena and ¹Department of Internal Medicine, Rheumatology Unit, Ospedale Maggiore, Bologna, Italy

Rheumatology 2001;40:158–169

Conclusion. At least in the medium term, both HY and MP modified a number of structural variables of the synovial membrane of the osteoarthritic human knee towards the appearance of that of normal synovium. The effect was more evident in primary OA than in OA secondary to a traumatic event. This is the first evidence that local hyaluronan injections modify the structural organization of the human knee synovium in OA.



Pain 130 (2007) 126–136

PAIN

www.elsevier.com/locate/pain

Nociceptive nerve activity in an experimental model of knee joint osteoarthritis of the guinea pig: Effect of intra-articular hyaluronan application

Ana Gomis ^{ab*}, Ana Miralles ^a, Robert F. Schmidt ^{ab}, Carlos Belmonte ^a

^a Instituto de Neurociencias de Alicante, Universidad Miguel Hernández-CSIC, 03550 Sant Joan d'Alacant, Spain
^b Physiologisches Institut der Universität Würzburg, Röntgenweg 9, D-97070 Würzburg, Germany

Hyaluronic acid reduces COMP release from arthritic cartilage

Takasaki, M, Fukushi, J, Iwamoto, Y.
+ Kyushu University Graduate School of Medicine, Orthopaedic surgery, Fukuoka, Japan
email address: fukushi@med.kyushu-u.ac.jp

Intra-Articular Hyaluronic Acid

Indication:

- Mild/Moderate OA of the knee
- 1 injection/week x 3-5 weeks

Benefits:

- Pain relief¹
- Decreased inflammation²
- Shown to be chondroprotective in animal models³

Excellent Safety Profile:

- No documented deaths and very few serious AEs in 13 years of use in US and 23 years of use worldwide use

Cost Effective:

- One course of treatment for 6 months duration

Potential Disease Modifier:

- May delay OA progression and decrease total joint burden

1. Gomis A, Miralles A, Schmidt R, et al. *Pain*. 2007;130:126-136.

2. Waddell DD, Kolomytkin OV, Dunn S, et al. *Clin Orthopaed Rel Res*. 2001;465:241-248.

3. Tang T, Muneta T, Ju YJ, et al. *Arthritis Res Ther*. 2008;10:1-8.

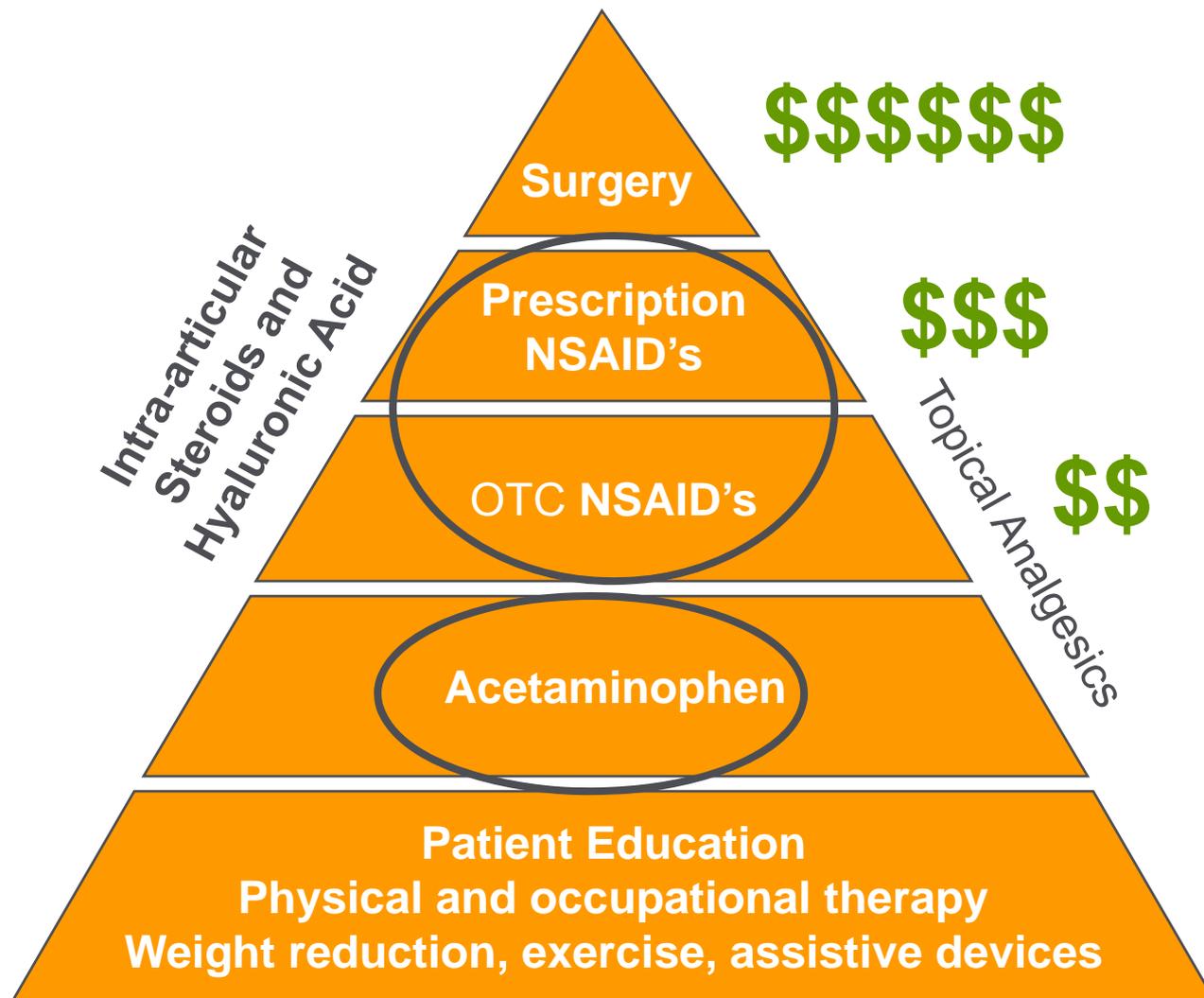
Conclusion

Corticosteroids may be an effective treatment tool for OA knee pain for some patients however:

- Their duration of effect is short compared to IA-HA
- The chondrotoxic effect on cartilage may actually hasten the cartilage degradation process pushing the patient to TKR earlier
- The danger of drug-drug interactions is high and CS use poses danger to certain patients such as diabetics
- IA-HA offers a safe, effective treatment for OA knee pain compared to alternative treatment options

Gary Myerson, MD

Widely Accepted Treatment Paradigm



NSAID Facts

- Only 1 in 5 who have a serious problem from NSAIDs have warning symptoms¹
- Non-selective NSAIDs account for at least 16,500 deaths and 103,000 hospitalizations annually in the U.S.²
- Four times more Americans die from NSAIDs annually than from cervical cancer²
- Approximately the same number of Americans die from NSAID toxicity as die from AIDS each year²
- Clinically important UGI events occur in 3- 4.5% of regular NSAID takers³
- In North America, the economic consequences of NSAID use results in \$0.66 to \$1.25 spent on UGI toxicities for each dollar spent on NSAIDs⁴

1. FDA. NSAID package insert labeling. Available at:

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106230.pdf>. Accessed January 2010., 2. Wolfe MM, et al. *N Engl J Med.* 1999;340:1888-1899. , 3. Laine L. *Gastroenterology.* 2001;120:594-606., 4. Laine L, Wogen J, Yu H. *Gastroenterology.* 2003;125:389-395.

NSAID Boxed Warnings

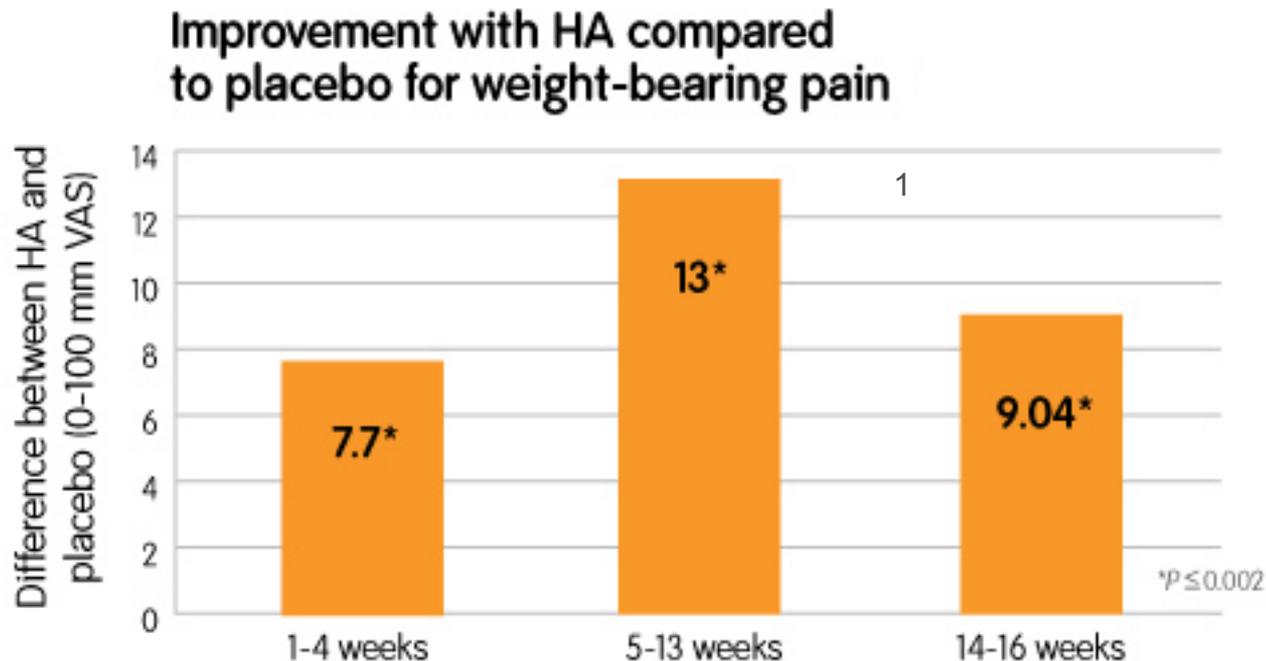
Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See **WARNINGS** and **CLINICAL TRIALS**).
- **TRADENAME** is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (See **WARNINGS**).

IA-HA Confirmed Effective

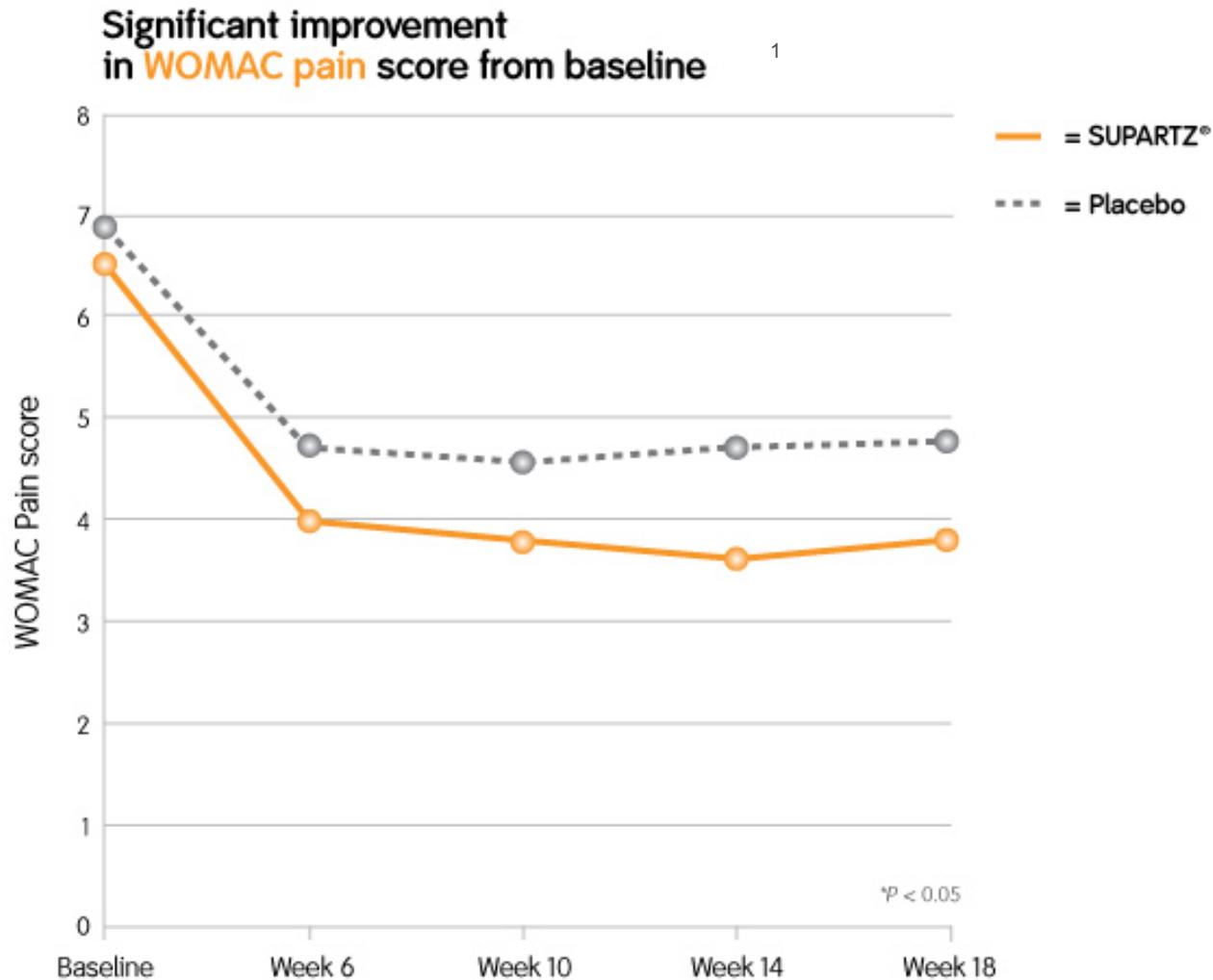


- The *Cochrane Review* demonstrates that HA provides a significant improvement in weight-bearing pain compared to placebo¹
- Additional meta-analyses have confirmed the results of Bellamy et al^{2,3}

1. Bellamy N, et al. *Cochrane Database Syst Rev*. 2006;(2):CD005321.
2. Lo GH, et al. *JAMA*. 2003;290(23):3115-3121.
3. Wang CT, et al. *J Bone Joint Surg Am*. 2004;86-A(3):538-545.

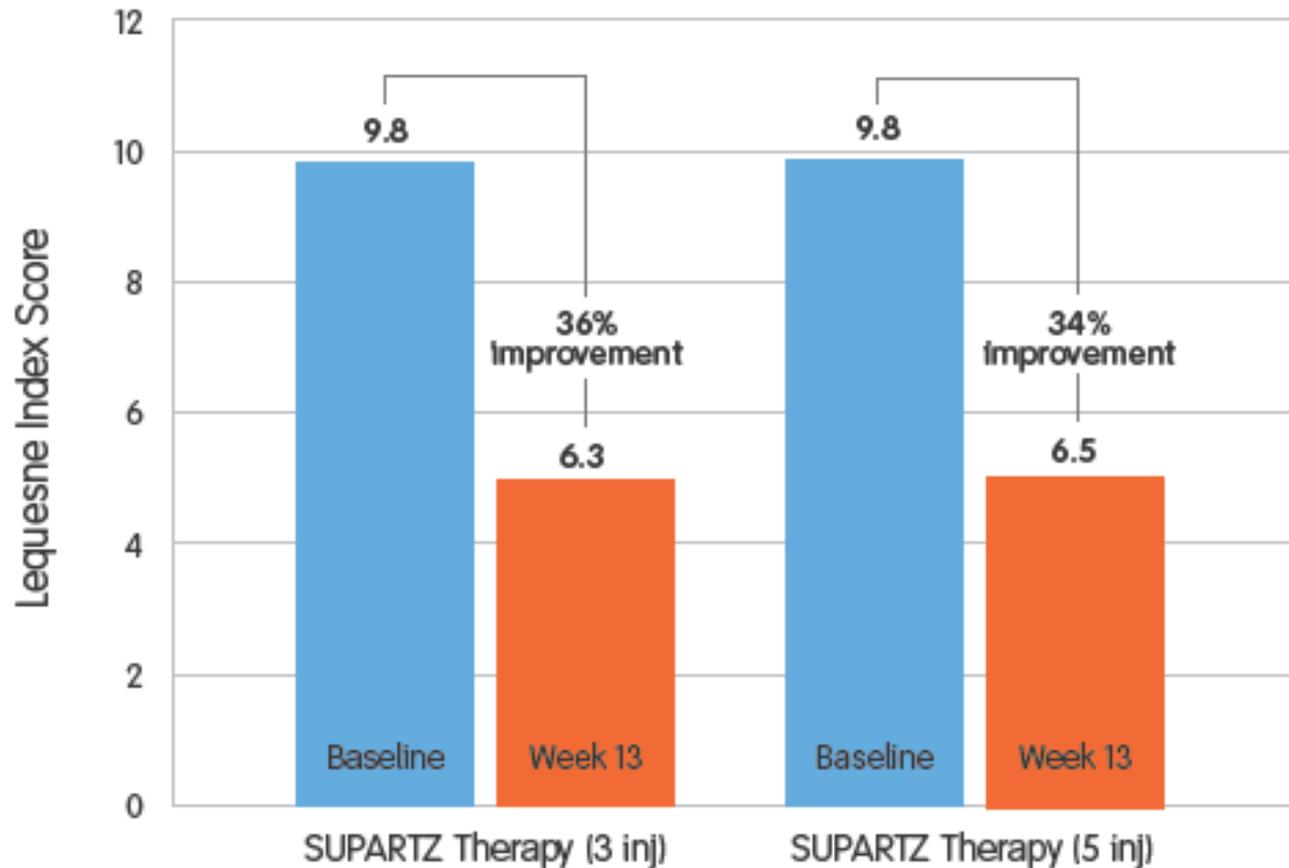
IA-HA Confirmed Effective¹

Change from Baseline



Supartz® FDA Label: Flexible Dosing

Improvements in **Lequesne Index** scores with 3 and 5 injections of SUPARTZ® Therapy



**Some patients experience benefit with as few as 3 injections*

Cost Effectiveness vs. NSAID/Gastroprotectant

Six Months Duration

Therapy	<u>SUPARTZ</u>	<u>Arthrotec</u>
Dosage	3	bid
Product Cost*	\$390	\$853
Administration	\$195	
Total	\$585	\$853

* WAC Cost: Medi-Span

Conclusion

- NSAIDs are an effective treatment tool for OA knee pain however chronic long term usage poses significant safety issues
- The costs of treatment with IA-HA is comparable to NSAID/Gastroprotectant treatment w/o consideration of treatment costs associated with NSAID adverse effects
- IA-HA offers a safe, effective treatment for OA knee pain compared to alternative treatment options

1.SUPARTZ [package insert]. Memphis, TN: Smith & Nephew, Inc; 2007; 2.Smith & Nephew internal market analysis of global HA sales from 1987 to October 2009; 3. Strand V, et al. Osteoarthritis Cartilage. 2006;14(9):859-866;

*Some patients may experience benefit with 3 injections given at weekly intervals. This has been noted in a study in which patients treated with 3 injections were followed for 90 days.



Agency Medical Director Comments

Hyaluronic Acid (HA) Injections for
Osteoarthritis (OA) of the Knee
WA State Agency Data



Agency Concerns

Safety (Low)

- Adverse events increase with number of treatment courses, generally safe

Efficacy (Medium)

- Unknown mechanism, unstudied duration; of sub-clinical average result; additive not alternative

Cost (High)

- Usage and costs escalating rapidly



Coverage Overview

- Currently covered by all WA state agencies.
 - DSHS/UMP cover without restrictions
 - LNI covers when:
 - OA of the knee retards recovery from accepted condition
 - Single course of injections only
 - After documented failure of all alternative therapies:
 - Non-pharmacological (e.g. physical therapy)
 - Non-opioid analgesics (acetaminophen)
 - 2 different NSAID classes

Utilization Data: Completion of Tx

COMBINED AGENCY DATA, 2008

2008 Injection Series	Hyalgan/ Supartz*	Synvisc	Euflexxa	Orthovisc	All Injection Types
Background info					
Total Patients 2008	596	686	163	411	1856
FDA Injection Counts per Procedure	5(3-5)*	3	3	3	
Series Completions					
Patients completing at least 1 series of injections	39%	72%	64%	71%	61%
Patients completing 2 series or more	4%	12%	7%	10%	
Series Incompletions					
Patients who did not complete any injection series	61%	27%	29%	24%	37%
Patients with a single injection only	16%	12%	15%	12%	
Patients with two injections only	11%	15%	15%	12%	
Three injection incomplete series (Hyalgan/Supartz only)	24%				
Four injection incomplete series (Hyalgan/Supartz only)	11%				

*Hyalgan (5 inj) and Supartz (3-5 inj) are combined due to a shared billing code. Completion data may be skewed by the proportion of each drug prescribed, the speed of adoption of FDA approved label changes in practice, and the severity of the patients' condition.



Utilization: Inconsistent Use

FDA inconsistent in injection count approval

- Supartz approved for 3, amended to 3 or 5 in 2006
- Orthovisc approved in 2004 for 3 or 4 injections

8-16% of UMP and DSHS patients using Synvisc or Euflexxa (3 injections) receive more injections than FDA approved treatment

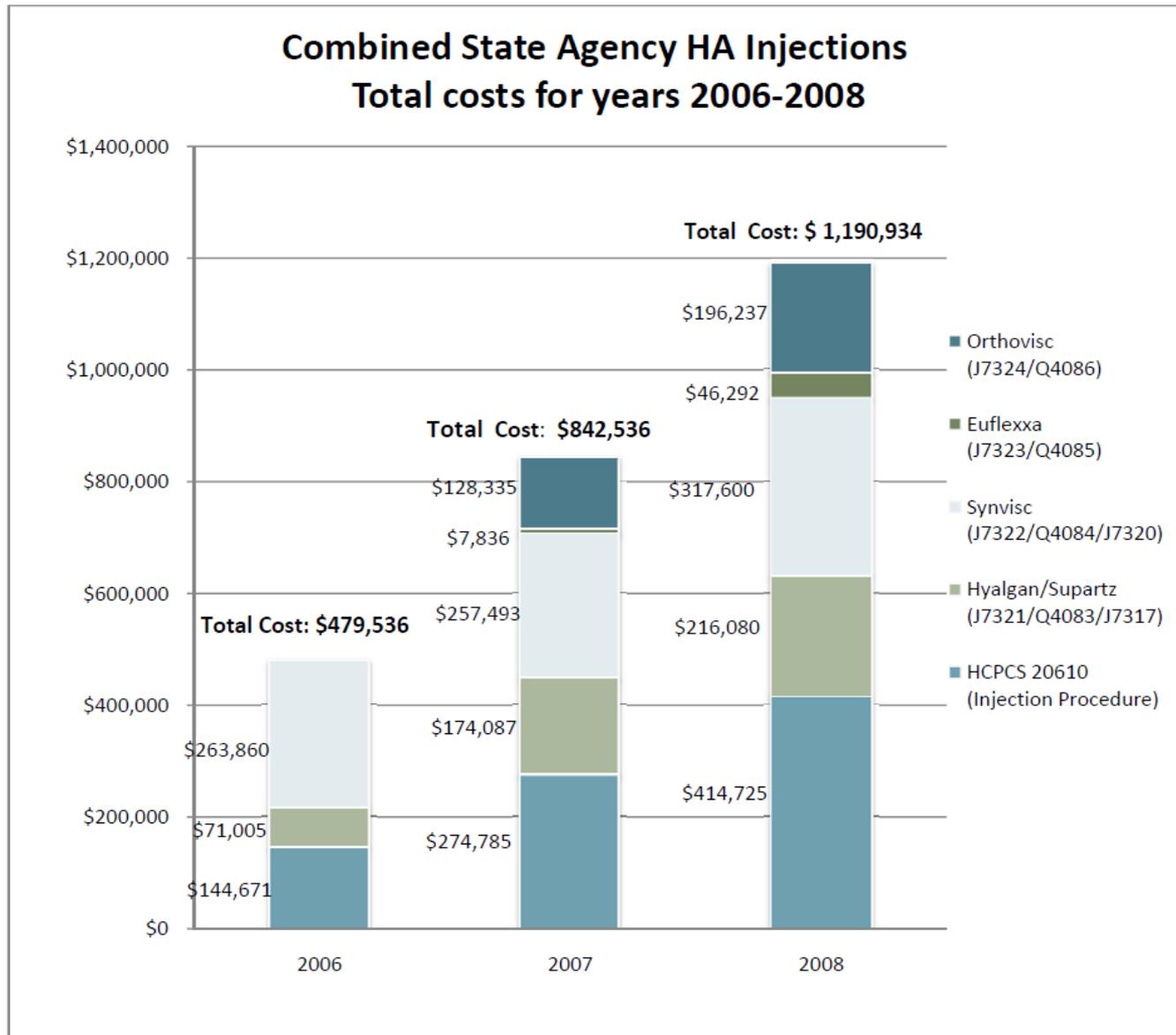
Agency HA Cost Experience

- Average \$838,000/year
- Costs escalating by 40% each year

UMP, L&I, DSHS DATA 2006-2008

2006-2008	Patient count	Procedure Count	Total Cost
Unified Medical Plan	1969	8424	\$1,201,323
Labor & Industry	934	2917	\$850,330
Dept of Social and Health Services	848	2780	\$461,353
All Agencies	3571	14121	\$2,513,006

A picture of escalating costs





Agency experience with products

HA products vary in cost

Agency payment data shows:

- Average injection payments range from \$55 to \$164 by product
- Evidence does not demonstrate superiority or difference in products

No apparent overlap with knee surgery

UMP DATA, 2006-2008

Year	HA Pt Counts by Year	General Knee Surgery Comparisons				Total Knee Replacement Comparisons			
		Counts		Percentages		Counts		Percentages	
		All KS Pts	HA Pts with KS	HA Pts with KS	KS Pts with HA	All TKA Pts	HA Pts with TKA	HA Pts with TKA	TKA Pts with HA
2006	376	567	149	40%	26%	43	12	3%	28%
2007	647	579	176	27%	30%	46	19	3%	41%
2008	942	1478	191	20%	13%	56	19	2%	34%

KS = Knee Surgery TKA = Total Knee Arthroplasty (Knee replacement)

***Notes:**

- UMP data is presented due to inability to link patients and claims for other agencies
- Analysis constrained to 2006-2008 due to approval of HA injections in 2006, and incomplete annual data unavailable after 2008.
- Short time frames for all procedures (HA, KS, TKA) reduces our ability to form linkages between events
- General estimated rate of turnover for plan beneficiaries is 30% annually
- Small populations for procedures may skew results



Scientific Evidence: Efficacy

- Despite 50+ trials, no large effect; no consistent clinically meaningful effect;
 - Statistically significant pain reduction in some patients

However:

- Study focus on pain reduction in short term: some equivalent to placebo, or NSAIDS;
- Inadequate evidence of functional improvement
- Inadequate long term studies and follow up
- Inadequate controls for other treatment
- Recent longer (26 wk) studies have found both exercise & ACS injections superior to HA



Safety Data

- Minor adverse events relatively common, increasing in frequency with repeated procedures
- Adverse events may be elevated with some product types
- Major adverse events are rare, but do occur
- Comparative safety advantage with NSAIDS (systemic) questionable as not used as alternative and relief from HA short term



Cost-effectiveness (CE) evidence

- No evidence of clinically significant improvement in outcomes; therefore, cost effective and economic studies are not appropriate
 - Current cost-effectiveness analysis unclear basis as clinically meaningful improvement not demonstrated
 - No high quality evidence that treatment is alternative, currently additive
 - No high quality evidence of number of patients with clinical improvement in pain and function
 - Assumption on duration of effect unclear



Bandolier Summary

- The evidence for a big effect is underwhelming. The evidence for any effect carries limited weight. The evidence is that there will be harm to be balanced against any small benefit....
- The real disappointment comes from the reporting.... Bandolier looks for outcomes that are more meaningful, like patients improved, or changes in a scale, or better still, some clinically useful but simply described outcome that we can understand.

www.medicine.ox.ac.uk/bandolier/band123/b123-4.html



AMD Recommendations

Non-coverage due to:

- Meaningful clinical effect on pain not demonstrated; low evidence on other patient outcomes
- Harms occur, usually minor, but include serious adverse event (pseudosepsis)
- Consistent with high quality guidelines weak to negative conclusions

If HTCC finds evidence suggestive of net health benefit, limit to:

- FDA Indications
- Require evidence of conservative management
- Limit number of treatment courses
- Leave product type to agency discretion



Viscosupplementation for Osteoarthritis of the Knee

Teresa Rogstad, MPH
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Hayes

Presentation Overview

- Background
- Methods
- Findings
- Guidelines
- General Conclusion
- Limitations of the Evidence

Background: Osteoarthritis

- Osteoarthritis (OA), ~ 27 million adults in the U.S.
- Most commonly affected joint is knee; prevalence 12%-16%
- Treatment
 - Physical therapy/exercise/weight loss
 - Acetaminophen→nonsteroidal antiinflammatory drugs (NSAIDs)→intraarticular (IA) corticosteroid→→total knee replacement (TKR)

Background: Hyaluronic Acid

- Names: Hyaluronic acid (HA), hyaluronan, sodium hyaluronate
- Alternative to NSAIDs, IA corticosteroid
- Natural substance in synovial fluid
 - Appears to deplete with OA
- Food and Drug Administration (FDA) approval
 - OA of the knee
 - Off-label: Hip, shoulder, ankle, temporomandibular joint, rheumatoid arthritis
 - Caution: Retreatment

The logo for Hayes, featuring the word "Hayes" in a bold, italicized, teal-colored sans-serif font. A thick teal horizontal bar is positioned behind the text, extending from the left edge of the slide to the right edge of the logo.

Background: Hyaluronic Acid (cont.)

- Marketed in the U.S.
 - Euflexxa® (Ferring) – Hyalgan® (Sanofi-Aventis) – Orthovisc® (Anika Therapeutics) – Supartz® (Seikagaku Corporation) – *Synvisc® (Genzyme)
- Different forms of HA
 - *Hylan GF-20: Cross-linked polymer; derivative of HA; *high* molecular weight
 - *Medium* molecular weight HA
 - *Low* molecular weight HA

Methods

- Patient group: Adults with OA of the knee
- Intervention(s): Viscosupplementation (hyaluronic acid injection – Hyalgan, Synvisc, Supartz, Orthovisc, Euflexxa)
- Comparator(s): NSAIDs, corticosteroid injection, physical therapy, oral pain medications, placebo, arthroscopic lavage and/or debridement
- Outcome(s): Pain, function, quality of life, adverse effects

Methods: Key Questions

- 1.a. What is the **clinical effectiveness** of viscosupplementation for treatment of OA of the knee?
- 1.b. Do different viscosupplementation products vary in effectiveness?
2. What are the **adverse effects** associated with viscosupplementation in patients with OA of the knee?
3. Does the effectiveness of viscosupplementation **vary by subpopulation** defined by these factors: age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), and prior treatments?
4. What are the **cost implications and cost-effectiveness** of this type of product?



Methods: Searches

- Usual MED Rapid Review process
- Core sources
- Literature databases
 - MEDLINE, Jan 2006 – Dec 2009; systematic reviews (SRs), technology assessments, and guidelines
 - MEDLINE and EMBASE, Sep 2009 – Dec 2009; primary studies after latest SR search
- Study design, primary studies: Randomized controlled trials (RCTs) only

Search Results

- 3 general systematic reviews (SRs)
 - Hayes Report (2009)
 - AHRQ Technology Assessment; review of 6 meta-analyses (MAs) plus supplemental analysis (Samson et al., 2007)
 - Cochrane Review with MA (Bellamy et al., 2006)
- 2 special-issue SRs with MA
 - Hylan vs HA (Reichenbach et al., 2007)
 - HA/hylan vs IA corticosteroid (Bannuru et al., 2009)
- 4 recent RCTs (late 2009)
- Various sources of cost/cost-effectiveness data

Placebo-Controlled RCTs

Source	Meta-analysis?	# of placebo-controlled RCTs	SR Quality	RCT Quality
Hayes 2009	No	11	Fair-good	No individual rankings
Samson 2007 (AHRQ)	Yes; reviewed 6 MAs; add'l new analyses	42 (5-32 per MA)	Good (Variable MA quality)	Good (9), fair (16), poor (12), not evaluable (5)
Bellamy 2006 (Cochrane)	Yes (included in Samson 2007)	32	Fair-good	No individual rankings
Altman 2009 Baltzer 2009	N/A; trials from primary lit	2	N/A	Good Good

Findings: Efficacy vs Placebo

(Moderate-quality evidence; ~50 RCTs, 6 MAs)

- Statistically significant differences in pain and function, esp. during ~1-2 months after treatment
- Benefit may not be clinically important
 - Pooled estimates of difference: < 20 points on 100-point scales (except hylan vs placebo)
 - Standardized effect sizes: 0.0-0.32; 0.80 in 1 MA
- Conflicting evidence, two 2009 primary RCTs
- Response rates (2 RCTs)
 - Nonsignificant in ITT analysis (Altman 1998)
 - 76% vs 62% ($P<0.03$) (Neustadt 2005)

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Randomized Comparator Trials

Comparison	Key Source	# trials	Quality of Source	Quality of Trials
HA vs NSAIDs	Bellamy 2006	6 total; 4 effectiveness and 2 safety	Fair-Good	Not individually assessed,
HA vs IA corticosteroid	Bannuru 2009 (Meta-analysis)	7	Good	Low
Hylan vs non-hylan HA	Reichenbach 2007 (Meta-analysis)	13	Good	Generally poor or incomplete reporting
HA vs conventional treatment	Hayes 2009	2 (Raynauld 2002; Kahan 2003)	Fair-Good	Not individually assessed.



Findings: HA vs Other Treatments (Low-quality evidence)

- Improvement comparable with NSAIDs (4 RCTs), fewer adverse events (2 RCTs)
- Longer-lasting benefit than IA corticosteroids (1 MA of 13 RCTs)
 - HA superior after first few weeks
 - Largest effect size 0.39 (95% CI, 0.18-0.59), 17-26 weeks
- Response rates (2 RCTs)
 - 62% vs 35% ($P=0.0001$); ITT analysis
 - 65% vs 40% ($P=0.0001$); ITT analysis

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Findings: Effectiveness by Product (Low-quality evidence)

- Hylan may have superior benefit over non-cross-linked HA; magnitude unlikely to be clinically important (1 MA of 13 comparator trials)
- No evidence of difference, low vs medium molecular weight (2 MAs of placebo-controlled trials)

Findings: Safety

(Moderate-quality evidence)

- Best estimate*: 2% (per injection) risk of local, transient reactions; serious reactions possible
- HA vs placebo: Similar
- HA vs corticosteroid: Unavailable
- Hylan vs non-hylan HA: Small absolute increase in overall risk
- Increasing risk with repeat courses of treatment*

*Evidence available only from studies of hylan.

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Findings: Effectiveness by Subpopulation (Low-quality evidence)

- Disease severity: Conflicting evidence
- Age, individual trials: Conflicting evidence
- Age, analysis of 20 trials: Younger age, greater efficacy (vs placebo)
- Race/ethnicity, gender, primary vs secondary OA, disease duration, weight, prior treatments:
 - Not studied *or*
 - 1 or 2 studies showed no relationship

Findings: Cost Implications

- \$65 to \$195 per injection (U.S. estimate)
- No cost-effectiveness conclusions
 - 2 randomized trials suggest acceptable cost effectiveness (Canada, France)
 - Celecoxib more cost-effective than HA as an alternative to naproxen in patients who have declined TKR (Taiwan)
 - Unknown representativeness of effectiveness estimates
 - May not apply to U.S.



Guidelines

- 3 high-quality guidelines
 - Weakly positive in favor of HA (OARSI)
 - No recommendation because of unclear clinical importance of benefit (AAOS)
 - Negative because of limited cost-effectiveness analysis (NICE)
- 3 poor-quality guidelines: Clinical option

Limitations of the Evidence

- Poorer-quality and smaller trials may have inflated estimates of efficacy.
- Variation in study methods.
- Few data on response rates, comparative effectiveness, and subpopulations.
- No safety data from large databases, except for hylan.
- No analysis of synergistic effects.
- No U.S. economic evaluations.

General Conclusion

- On average, improvement in pain and function (most relief during 1-2 months after treatment).
- Magnitude of benefit may be too small to be clinically important.
- Safety risks small, generally nonserious.

Practice Considerations

- Longer- lasting benefit compared with intraarticular corticosteroids (low-quality evidence).
- Potential alternative to NSAIDs after simpler treatments have failed or next step after NSAIDs have failed (assumed roles in cost-effectiveness studies; sparse evidence)
- Ability to avert total knee replacement has not been studied



Thank you. Questions?

Hayes

HTCC Coverage and Reimbursement Determination Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on these questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are Evidence based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective¹ as expressed by the following standards.²

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms.³

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.
- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

¹ Based on Legislative mandate: See RCW 70.14.100(2).

² The principles and standards are based on USPSTF Principles at: <http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm>

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Using Evidence as the basis for a Coverage Decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. *Availability of Evidence:*

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. *Sufficiency of the Evidence:*

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence⁴ using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- the amount of evidence (sparse to many number of evidence or events or individuals studied);
- consistency of evidence (results vary or largely similar);
- recency (timeliness of information);
- directness of evidence (link between technology and outcome);
- relevance of evidence (applicability to agency program and clients);
- bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

3. *Factors for Consideration - Importance*

At the end of discussion at vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- risk of event occurring;
- the degree of harm associated with risk;
- the number of risks; the burden of the condition;
- burden untreated or treated with alternatives;
- the importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- the degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- value variation based on patient preference.

⁴ Based on GRADE recommendation: <http://www.gradeworkinggroup.org/FAQ/index.htm>

Medicare Coverage and Guidelines

Organization	Date	Outcome	Evidence Cited?	Grade / Rating
(CMS)		No National Coverage Decision		
Guidelines – WA HTA Page: 34 & 67 <i>Osteoarthritis Research Society International (OARSI)</i>	2008	Injections of intraarticular hyaluronate may be useful in patients with knee OA (level of evidence Ia; strength of recommendation 64% (95% CI, 43-85). They are characterized by delayed onset, but prolonged duration, of symptomatic benefit when compared with intraarticular injections of corticosteroids.	Systematic search of MEDLINE, EMBASE, CINAHL, AMED, and Science Citation Index identified 9 guidelines and 6 systematic reviews pertaining to viscosupplementation (23 guidelines and 40 studies total for the whole guideline).	Good
Guidelines – WA HTA Page: 34 & 67 <i>American Academy of Orthopaedic Surgeons (AAOS)</i>	2008	AAOS concluded that they could not recommend for or against the use of intraarticular hyaluronic acid for patients with mild to moderate symptomatic OA of the knee (level of evidence I and II; grade of recommendation inconclusive).	AHRQ (2007) evidence report served as the basis for this recommendation; the systematic review in the AHRQ (2007) report included 6 meta-analyses (41 RCTs) and 1 additional RCT.	Good
Guidelines – WA HTA Page: 34 & 67 <i>National Institute for Clinical Health & Excellence (NICE)</i>	2008	Intraarticular hyaluronan injections are not recommended for the treatment of OA of the knee, or any other joint.	Evidence from 1 Cochrane systematic review with meta-analysis in patients with OA of the knee (40 RCTs) and 3 additional RCTs was basis for the recommendation.	Good
Guidelines – WA HTA Page: 34 & 67 <i>Veterans Health Administration</i>	2008	Evidence supports the use of intraarticular hyaluronan or hylan injections for OA of the knee.	MEDLINE literature search with unclear methodology; 7 systematic reviews with meta-analyses included as evidence.	Poor
Guidelines – WA HTA Page: 34 & 67 <i>American College of Rheumatology (ACR)</i>	2000	Intraarticular hyaluronan therapy is indicated for use in patients who have not responded to a program of nonpharmacological therapy and simple analgesics. Intraarticular hyaluronan injections may be especially advantageous in patients in whom nonselective NSAIDs and COX-2 specific inhibitors are contraindicated, or in whom they have been associated either with a lack of efficacy or with adverse events.	Evidence used in guideline, but no clear methodology provided.	Poor
Guidelines – WA HTA Page: 34 & 67 <i>American Pain Society (APS)</i>	2002	“The injection of HA supplements into the knee may be considered in persons with OA and knee pain who are unresponsive to acetaminophen, nonselective and COX-2 selective NSAIDs, or who cannot take these medications.”	None described.	Poor

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

Discussion Document: What are the key factors and health outcomes and what evidence is there?

Hyaluronic Acid / Viscosupplementation³	
Safety Outcomes	Safety Evidence
Mortality	
Morbidity -- Minor complications -- Major complications	
Efficacy – Effectiveness Outcomes	Efficacy / Effectiveness Evidence
Pain Reduction - Scale; magnitude - term or duration	
Improves Function - Range of motion	
Patient Satisfaction / Quality of life	
Alternative or additive Treatment(s)	
Delay of Surgery (if yes, length)	
Product Type Variation	
Number of Injections	
Other	
Special Population / Considerations Outcomes	Special Population Evidence
Age	
Race / Ethnicity	
Gender	
Osteoarthritis (primary versus secondary)	
Weight (BMI)	
Disease Severity and Duration	
Prior Treatments	
Other	
Cost	Cost Evidence
Product Costs	
Cost effectiveness	

Clinical Committee Evidence Votes

First voting question

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Is there sufficient evidence under some or all situations that the technology is:

	Unproven (no)	Equivalent (yes)	Less (yes)	More (yes)
Effective				
Safe				
Cost-effective				

Discussion

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second vote

Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is

_____ Not Covered. _____ Covered Unconditionally. _____ Covered Under Certain Conditions.

Discussion Item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Clinical Committee Findings and Decisions

Next Step: Cover or No Cover

If not covered, or covered unconditionally, the Chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next Step: Cover with Conditions

If covered with conditions, the Committee will continue discussion.

- 1) Does the committee have enough information to identify conditions or criteria?
 - Refer to evidence identification document and discussion.
 - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
 - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.
- 2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
 - What are the known conditions/criteria and evidence state
 - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Efficacy Considerations:

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
 - Direct outcome or surrogate measure
 - Short term or long term effect
 - Magnitude of effect
 - Impact on pain, functional restoration, quality of life
 - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy
 - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
 - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
 - Adverse effect on health that can result in lasting harm or can be life-threatening.
- Other morbidity concerns
- Short term or direct complication versus long term complications
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost Impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?