Washington State Health Care Authority
Health Technology Assessment

## Hyaluronic Acid/ Viscosupplemenation

### Order of Scheduled Presentations

| | Name | Representing | Notes |
|---|---|---|---|
| 1 | Dr. Ghislaine Robert, M.D | Fidia Pharma USA Inc | No slides |
| 2 | Vinod Dasa MD | Department of Orthopaedic Surgery<br>Louisiana State University Health Sciences Center | |
| 3 | Michael W Schucker MS, PAS, PA-C | Rockwood Clinic Bone & Joint Center | No slides. |
| 4 | Jon E Block, PhD | The Jon Block Group | |
| 5 | Samir K Bhattacharyya, PhD | Mitek Sports Medicine/ DePuy Synthes | |
| 6 | Greg Devereux, Executive Director | WA Federation of State Employees | Letter. |

## Disclosure

Any unmarked topic will be considered a "Yes"

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
| 1. | Salary or payments such as consulting fees or honoraria in excess of $10,000. | | ✓ |
| 2. | Equity interests such as stocks, stock options or other ownership interests. | | ✓ |
| 3. | Status or position as an officer, board member, trustee, owner. | | ✓ |
| 4. | Loan or intellectual property rights. | | ✓ |
| 5. | Research funding. | | ✓ |
| 6. | Any other relationship, including travel arrangements. | | ✓ |

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
| 7. | Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government). | | ✓ |

If yes to #7, provide name and funding Sources:

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X Ghislaine Robert 10/23/2013 GHISLAINE ROBERT

*Signature* *Date* *Print Name*

**For questions contact:** Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126

## Disclosure

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| | Potential Conflict Type | Yes | No |
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| 1. | Salary or payments such as consulting fees or honoraria in excess of $10,000. | ✓ | |
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| 4. | Loan or intellectual property rights. | | ✓ |
| 5. | Research funding. | | ✓ |
| 6. | Any other relationship, including travel arrangements. | ✓ | |

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

BIOVENTUS

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
| 7. | Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government). | | ✓ |

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X _____ 10/3/13 VINOD DASA

*Signature* *Date* *Print Name*

**For questions contact:** Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126

# Vinod Dasa MD

Associate Professor
LSU Dept of Orthopedic Surgery
New Orleans, LA

# The challenge

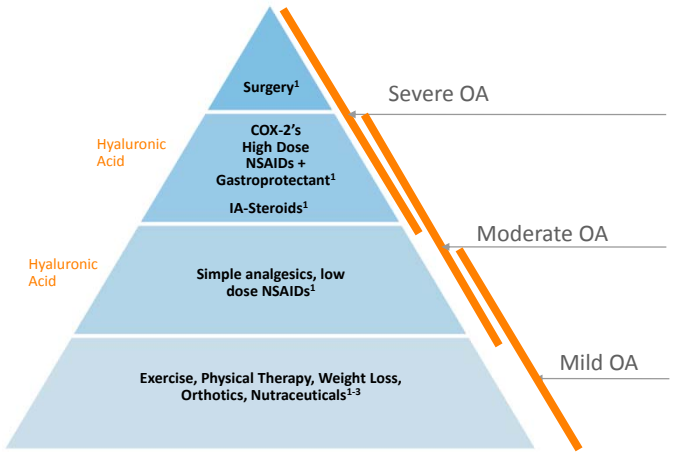
APAP/Ibuprofen

reflux/ulcers, warfarin, clopidogrel, renal disease…

Intra-articular Steroids

Arthroplasty

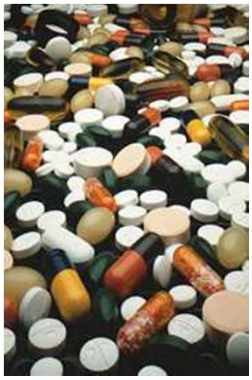
# Managing knee OA




1. Adapted from: ACR. Recommendations for the medical management of osteoarthritis of the hip and knee 2000. Available at: www.rheumatology.org. Accessed January 2010.
2. Marks R Penton L. *Int J Clin Pract*. 2004;58:49-57.
3. Mayo Clinic. Osteoarthritis. Available at: www.mayoclinic.org. Accessed January 2010.

# Medication

- NSAIDs
  - Aspirin
  - Ibuprofen
  - Naproxen
  - GI and CVS effects
- Narcotics

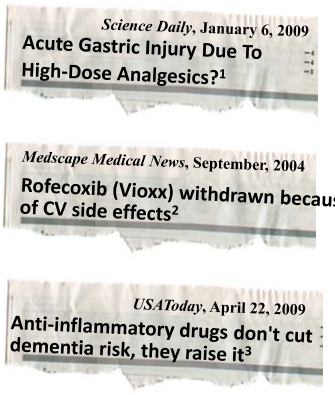


# NSAID Facts

- Causes hypertension[1]
- Only 1 in 5 who have a serious problem from NSAIDs have warning symptoms[1]
- 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 cancer[2]
- Approximately the same number of Americans die from NSAID toxicity as die from AIDS each year[2]
- Clinically important UGI events occur in 3- 4.5% of regular NSAID takers[3]
- 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 NSAIDs[4]

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.

# Systemic Considerations of NSAIDs





1. Science Daily. Available at: www.sciencedaily.com/releases/2008/12/081229104511.htm. Accessed January 2010.
2. Medscape Medical News. Available at: www.medscape.com/viewarticle/537940. Accessed January 2010.
3. Marcus MB. USAToday. Available at: www.usatoday.com/news/healt/2009-04-22-nsaid-dementia-N.htm. Accessed January 2010.

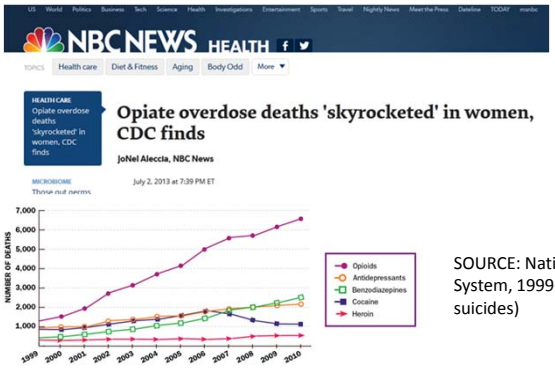
# Narcotics

Narcotics use in severe OA results in worse outcomes post-TKR[2]

The Journal of Arthroplasty Vol. 25 No. 6 Suppl. 1 2010

**Reduction in Narcotic Use After Primary Total Knee Arthroplasty and Association with Patient Pain Relief and Satisfaction**

Patricia D. Franklin, MD, MBA, MPH,* John A. Karbassi, MD, MPH,* Wenjun Li, PhD,† Wenyun Yang, MS,* and David C. Ayers, MD*




SOURCE: National Vital Statistics System, 1999-2010 (deaths include suicides)

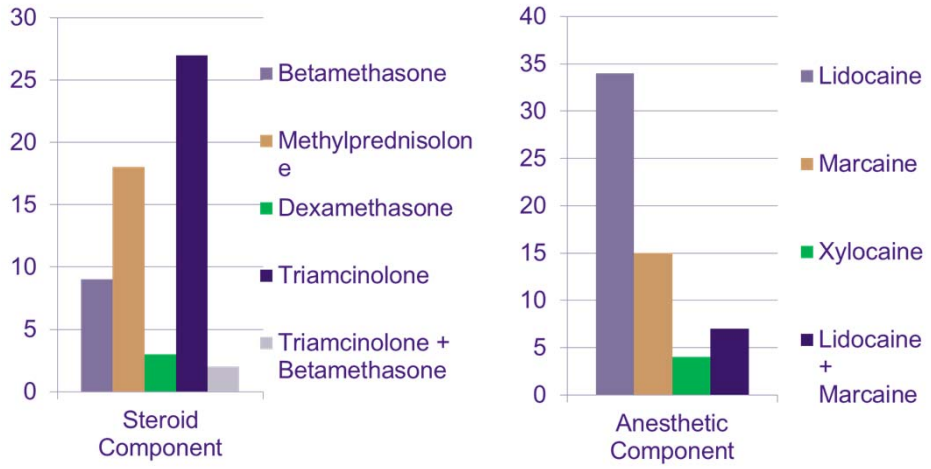
1. Rubin R. USAToday. Available at: www.usatoday.com/news/healt/2003-11-17-pill-usat-X.htm. Accessed January 2010.
2. Karbassi JA, Franklin PD, Li W, Yang W, Ayers DC. Reduction in Narcotic Use After Primary Total Knee Arthroplasty and Association with Patient Pain Relief and Satisfaction. J Arthroplasty 2009. Abstract 12.



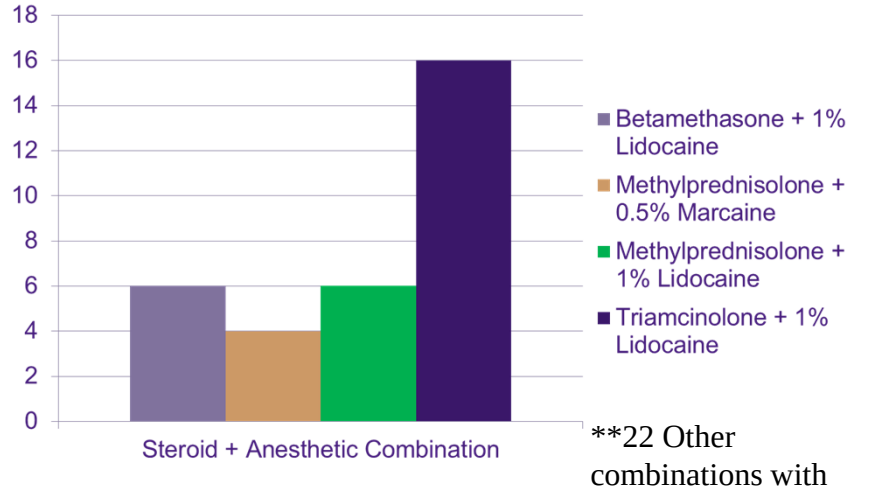
# Steroid injections

- Mod/severe OA
- Crystalline form (triamcinolone) provides slower absorption and longer effect than soluble forms (betamethasone)
- 3-4 injections/year
- Rare, self limited steroid synovitis and/or post steroid flare

## Steroid Cocktail Components Used By Louisiana Orthopaedic Surgeons




## Most Common Corticosteroid/Anesthetic Combinations




**22 Other combinations with frequency of 2 or less

# Steroid injections

- Pain relief within 24-48 hrs
- Lasts up to 6 weeks (maybe longer)

RELATIVE EFFICACY OF HYALURONIC ACID VERSUS CORTICOSTEROIDS IN THE TREATMENT OF KNEE OSTEOARTHRITIS: META-ANALYSIS

- DM- ↑ Blood glucose (returns to normal in 24 hrs)

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

# Corticosteroids: Chondrotoxicity

Lidocaine Potentiates the Chondrotoxicity of Methylprednisolone

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

*Arthroscopy: The Journal of Arthroscopic and Related Surgery, Vol 25, No 4 (April), 2009: pp 337-347*

Clin Orthop Relat Res (2010) 468:3112–3120
DOI 10.1007/s11999-010-1443-0

BASIC RESEARCH

Increased Chondrocyte Death after Steroid and Local Anesthetic Combination

Boglárka Farkas MD, Krisztián Kvell MD, PhD, Tamás Csimpöly MD, PhD, Tamás Illés MD, PhD, Tamás Bárdos MD, PhD

ELSEVIER

Journal of Orthopaedic Research

Corticosteroids alter the differentiated phenotype of articular chondrocytes

Susan L. Fubini [a], Rory J. Todhunter [a], Nancy Burton-Wurster [b], Margaret Vernier-Singer [a], James N. MacLeod [c,*]

Comparison of Ropivacaine and Bupivacaine Toxicity in Human Articular Chondrocytes

Samantha L. Piper and Hubert T. Kim
*J Bone Joint Surg Am.* 2008;90:986-991. doi:10.2106/JBJS.G.01033

In Vitro Cytotoxic Effects of Benzalkonium Chloride in Corticosteroid Injection Suspension

Daniel Davis, Mathew Cyriac, Dongxia Ge, Zongbing You and Felix H. Savoie
*J Bone Joint Surg Am.* 2010;92:129-137. doi:10.2106/JBJS.H.01561

In Vitro Exposure to 0.5% Bupivacaine Is Cytotoxic to Bovine Articular Chondrocytes

Constance R. Chu, M.D., Nicholas J. Izzo, Ph.D., Nicole E. Papas, B.S., and Freddie H. Fu, M.D.

*Arthroscopy: The Journal of Arthroscopic and Related Surgery, Vol 22, No 7 (July), 2006: pp 693-699*

Lidocaine Exhibits Dose- and Time-Dependent Cytotoxic Effects on Bovine Articular Chondrocytes In Vitro

John C. Karpie and Constance R. Chu
*Am J Sports Med* 2007 35: 1621 originally published online July 30, 2007
DOI: 10.1177/0363546507304719

LSUHSC Dept of Orthopedics©

# Steroids: Ligament/tendon

**Effects of local injection of corticosteroids on the healing of ligaments. A follow-up report**

ME Wiggins, PD Fadale, MG Ehrlich and WR Walsh
*J Bone Joint Surg Am.* 1995;77:1682-1691.

**The Effects of Dexamethasone on Human Patellar Tendon Stem Cells: Implications for Dexamethasone Treatment of Tendon Injury**

Jianying Zhang, Camille Keenan, James H-C. Wang

JOURNAL OF ORTHOPAEDIC RESEARCH JANUARY 2013

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.†

Number 123
March-April, 1977 Clinical Orthopaedics and Related Research

LSUHSC Dept of Orthopedics©

# Intraarticular Injections

Mild/mod OA, young patient → Kenalog / marcaine / lidocaine = future problems?

Chondrolysis of the Glenohumeral Joint After Infusion of Bupivacaine Through an Intra-articular Pain Pump Catheter: A Report of 18 Cases

S. Lance Anderson, M.D., F.R.C.S.C, Jordan Z. Buchko, B.Sc., M.D., Mario R. Taillon, M.D., F.R.C.S.C, and Mark A. Ernst, M.D., F.R.C.S.C

*Arthroscopy: The Journal of Arthroscopic and Related Surgery, Vol 26, No 4 (April), 2010: pp 451-461*

Google chondrolysis Search Advanced Search

Web Show options... Results 1 - 10 of about 114,000 for chondrolysis. (0.13 secon

Chondrolysis Lawsuit
www.ShoulderPainPumpLitigation.com Chondrolysis from a pain pump? Contact our law firms today.

Pain Pump Registry
www.Pain-Pump-Lawsuits.com Shoulder Pain? Pain Pumps Can Cause Damage. Register Your Complaint.

Pain Pump - Chondrolysis
painpump.jvglaw.com Law firm represents people with PAGCL after shoulder surgery.

Chondrolysis
The destruction of articular cartilage is known as chondrolysis. While chondrolysis is rare anywhere in the body, it has been most common in the hip when ...
www.chondrolysis.com/ - Cached - Similar

Sponsored Links

Sponsored Links

Shoulder Pain Pump Lawyer
Pain Pumps used in shoulder surgery linked to severe joint damage.
www.wdolaw.com

Pain Pump & PAGCL Lawsuit
PAGCL destroys cartilage in joint. Contact Us for a Free Consultation
Milberg.Biz/ShoulderPump.html

See your ad here »

## Disclosure

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| | Potential Conflict Type | Yes | No |
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| 5. | Research funding. | | |
| 6. | Any other relationship, including travel arrangements. | | |

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

FERRING PHARMACEUTICALS (EUFLEXXA)

* PLEASE SEE PAGE 3 ATTACHED *

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
| 7. | Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government). | | |

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I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X MS-PAC, PA-C 10/21/13 MICHAEL SCHUCREN

*Signature* *Date* *Print Name*

**For questions contact:** Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126

**Dear HTCC Workgroup Committee,**

I understand that the HTCC Workgroup is a public service workgroup established to safeguard the public interest by identifying medical tests and treatments where evidence shows they are safe, effective, and cost-effective. Balance, independence, objectivity and scientific rigor are a basis for public trust and crucial to the credibility and integrity of decisions. Attached is the Conflict of Interest that I have been required to sign prior to my verbal testimony. I personally would like to expand on my attestation when concerning this form, because I believe that I am in a unique situation with regards to the consultation, honoraria fees that I receive from the company (Ferring Pharmaceuticals) disclosed on my participant conflict disclosure. I do, as stated on the form receive consulting fees, and honoraria in excess of $10,000.00 from Ferring Pharmaceuticals (Euflexxa), but I think the committee should understand that I actually make less monetarily performing these services than I would as a physician assistant in my current orthopedic practice. The services that I perform for Ferring Pharmaceuticals do not compensate me in any way for time away from home/family, inconvenience of traveling, lost income due to reduced clinic hours/days, and having to use vacation time to make myself available for programs requiring significant travel time. As I have told the people of Ferring, I consult and do these programs because I have seen personally how hyaluronate does benefit a significant number of patients, is a non-surgical option for treating osteoarthritis of the knee, and for some, changes their life for the better. With this being said in all honesty I believe that I pose no potential conflict of interest on the subject of hyaluronate, all I sincerely want is the best possible treatments, modalities, and outcomes for all patient populations across the board.

Respectfully submitted,

10/21/13

Michael W. Schucker, MS PAS, PA-C
Rockwood Clinic Bone and Joint Center
Spokane, Washington

## Disclosure

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| | Potential Conflict Type | Yes | No |
|---|---|---|---|
| 1. | Salary or payments such as consulting fees or honoraria in excess of $10,000. | X | |
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| 3. | Status or position as an officer, board member, trustee, owner. | | X |
| 4. | Loan or intellectual property rights. | | X |
| 5. | Research funding. | | X |
| 6. | Any other relationship, including travel arrangements. | X | |

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

HA Viscosupplement Coalition

#6: Travel arrangements only (air, hotel)

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
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X Jon Block _____ Jon Block _____

*Signature* *Date* 10/25/13 *Print Name*

**For questions contact:** Christine Masters
Health Technology Assessment
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Olympia, WA 98504-2712
360-725-5126

# US-Approved Intra-Articular Hyaluronic Acid Injections are Safe and Effective in Patients with Knee Osteoarthritis: Systematic Review and Meta-Analysis of Randomized, Saline-Controlled Trials

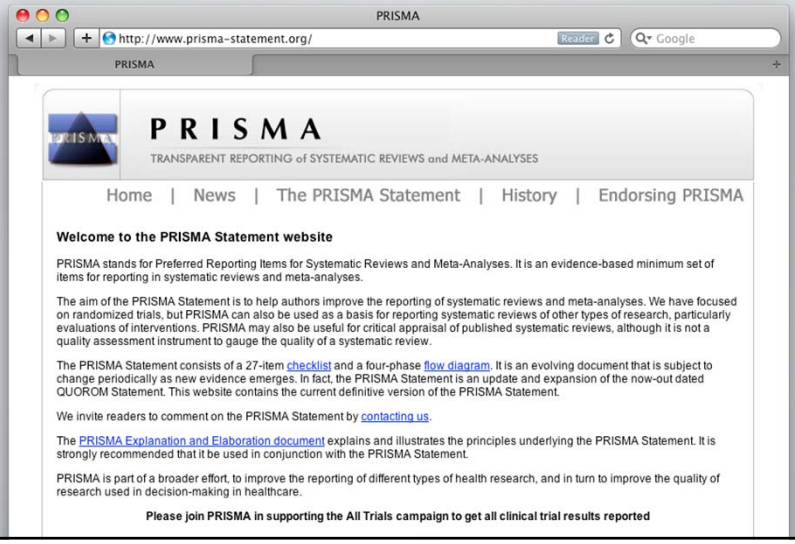
*Larry E. Miller and Jon E. Block*

*Clin Med Insights Arthritis Musculoskelet Disord. 2013 Sep 1;6:57-63.*

Presented by Jon E. Block Ph.D.
*Founder & President of the Jon Block Group*

the Jon Block Group
JONBLOCKGROUP.COM

## Conducted and Reported Using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)




2

# Inclusion Criteria:

- Injection of a US-approved HA product
- Randomized, sham-control study design
- Primary diagnosis of knee OA
- Identical treatment and follow-up conditions between IAHA and sham-control groups
- And at least one extractable efficacy or safety outcome

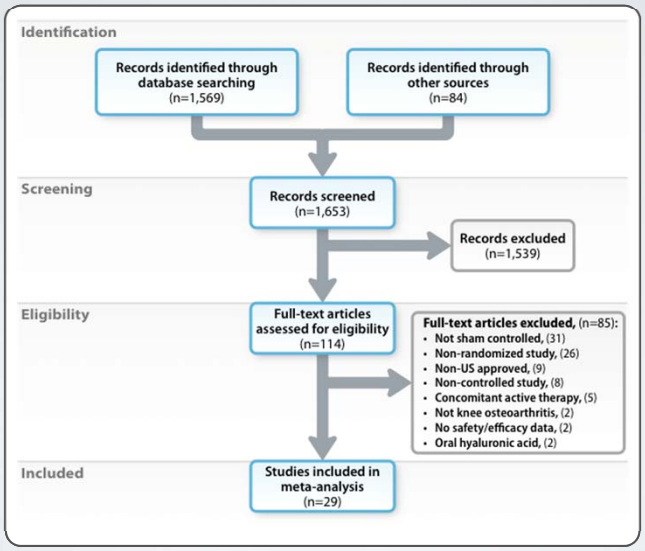
3

# Exclusion Criteria:

- Concomitant interventional therapies were uniformly administered
- The study was published in a non-English language journal
- Or if data were available only from:
  - Abstracts
  - Conference proceedings
  - Websites
  - Or personal communication

4

# PRISMA Flow Diagram




5

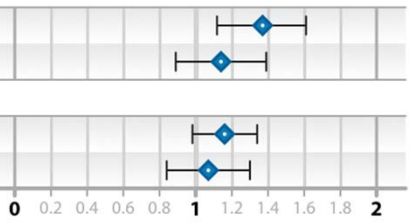
# Baseline Patient Characteristics

| Characteristic | IAHA | Saline |
|---|---|---|
| **Patients,** *n* | 2,673 | 2,193 |
| **Age,** *yr, mean (min–max)* | 65 (53–72) | 62 (53–73) |
| **Female gender,** *%, median (min–max)* | 64 (27–92) | 65 (22–100) |
| **Body mass index,** *kg/m², mean (min–max)* | 28 (25–32) | 29 (25–33) |
| **Symptom duration,** *yr, mean (min–max)* | 4.5 (1.0–9.1) | 4.3 (0.8–8.5) |
| **Kellgren-Lawrence grade,** *median (min–max)* | 2.5 (1.9–3.0) | 2.5 (1.8–3.5) |

6

# Standardized Mean Difference for Pre-to-Post Efficacy Changes with IAHA Injection

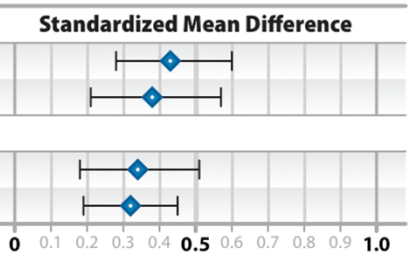
| Pain | SMD | 95% CI | P-value | Standardized Mean Difference |
|---|---|---|---|---|
| • 4 to 13 weeks | 1.37 | 1.12 to 1.61 | <0.001 | |
| • 14 to 26 weeks | 1.14 | 0.89 to 1.39 | <0.001 | |
| **Function** | | | | |
| • 4 to 13 weeks | 1.16 | 0.99 to 1.34 | <0.001 | |
| • 14 to 26 weeks | 1.07 | 0.84 to 1.30 | <0.001 | |




7

# Standardized Mean Difference for IAHA Injection vs. Saline Controls

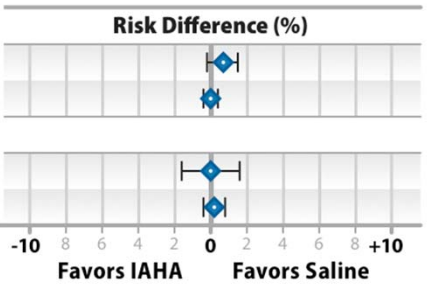
| Pain | SMD | 95% CI | P-value | Standardized Mean Difference |
|---|---|---|---|---|
| • 4 to 13 weeks | 0.43 | 0.26 to 0.60 | <0.001 | |
| • 14 to 26 weeks | 0.38 | 0.21 to 0.55 | <0.001 | |
| **Function** | | | | |
| • 4 to 13 weeks | 0.34 | 0.16 to 0.51 | <0.001 | |
| • 14 to 26 weeks | 0.32 | 0.18 to 0.45 | <0.001 | |




8

## Risk Difference in Safety Outcomes for IAHA Injection vs. Saline Controls

| SAE | RD (%) | 95% CI (%) | P-value |
|---|---|---|---|
| • Any | 0.7 | -0.2 to 1.5 | 0.12 |
| • Treatment-related | 0 | -0.4 to 0.4 | 1.00 |
| **Withdrawal** | | | |
| • Any | 0 | -1.6 to 1.6 | 1.00 |
| • AE-related | 0.2 | -0.4 to 0.8 | 0.46 |




9

## Saline-corrected Efficacy & Safety Outcomes Comparing US-approved vs. Non-US approved Viscosupplements

| Variable | US Approved? Yes | US Approved? No | p-Value |
|---|---|---|---|
| | *SMD* | | |
| **Pain** | | | |
| • 4 to 13 weeks | 0.42 | 0.11 | 0.07 |
| • 14 to 26 weeks | 0.38 | 0.26 | 0.50 |
| **Function** | | | |
| • 4 to 13 weeks | 0.32 | -0.02 | 0.048 |
| • 14 to 26 weeks | 0.32 | 0.10 | 0.20 |
| | *Risk Difference (%)** | | |
| **Safety** | | | |
| • SAE | 0.7 | 0.2 | 0.52 |
| • Treatment-related SAE | 0.0 | 0.0 | 1.00 |
| • Withdrawal | 0.0 | 0.3 | 0.87 |
| • Withdrawal due to AE | 0.2 | 1.2 | 0.33 |

10

# Subgroup Analysis of Study- and Patient-related Factors on Saline-corrected Knee Pain

| Factor | SMD | 95% CI | p-Value |
|---|---|---|---|
| **Total sample size** | | | |
| • ≥ 100 (n=14) | 0.17 | 0.01 to 0.33 | <0.001 |
| • < 100 (n=20) | 0.67 | 0.47 to 0.86 | |
| **Jadad score** | | | |
| • ≥ 3 (n=30) | 0.34 | 0.20 to 0.48 | 0.03 |
| • < 3 (n=4) | 0.87 | 0.42 to 1.33 | |

No other factors including age, body mass index, female gender proportion, symptom duration, Kellgren-Lawrence grade, or industry funding were statistically significant.

11

# Subgroup Analysis of Study- and Patient-related Factors on Saline-corrected Knee Function

| Factor | SMD | 95% CI | p-Value |
|---|---|---|---|
| **Female gender proportion** | | | |
| • ≥ 67% (n=9) | 0.63 | 0.36 to 0.89 | 0.01 |
| • < 67% (n=15) | 0.25 | 0.10 to 0.39 | |
| **Total sample size** | | | |
| • ≥ 100 (n=13) | 0.22 | 0.08 to 0.35 | 0.001 |
| • < 100 (n=11) | 0.69 | 0.44 to 0.93 | |
| **Jadad score** | | | |
| • ≥ 3 (n=21) | 0.28 | 0.15 to 0.40 | 0.002 |
| • < 3 (n=3) | 1.05 | 0.57 to 1.52 | |

No other factors including age, body mass index, symptom duration, Kellgren-Lawrence grade, or industry funding were statistically significant.

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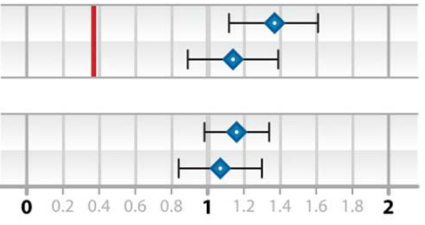
# Standardized Mean Difference for Pre-to-Post Efficacy Changes with IAHA Injection

| Pain | SMD | 95% CI | P-value |
|---|---|---|---|
| • 4 to 13 weeks | 1.37 | 1.12 to 1.61 | <0.001 |
| • 14 to 26 weeks | 1.14 | 0.89 to 1.39 | <0.001 |
| **Function** | | | |
| • 4 to 13 weeks | 1.16 | 0.99 to 1.34 | <0.001 |
| • 14 to 26 weeks | 1.07 | 0.84 to 1.30 | <0.001 |

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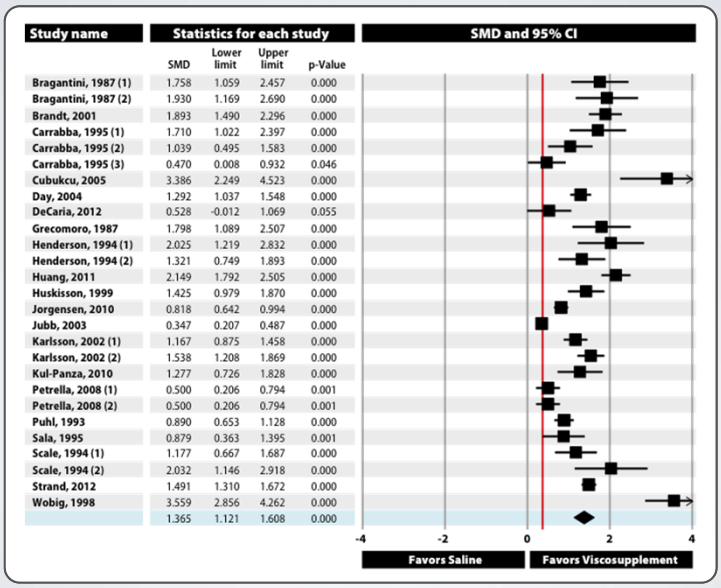
# Viscosupplementation on Knee Pain at 4 to 13 Weeks vs. Pre-Treatment

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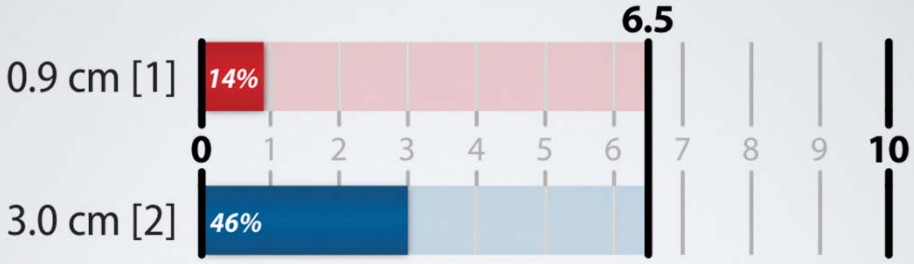
# VAS Extrapolation




***The accepted MCID is 2.0 cm or 30%.***

[1] Ann Intern Med. 2012 Aug 7;157(3):180-91.
[2] Clin Med Insights Arthritis Musculoskelet Disord. 2013 Sep 1;6:57-63.

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THANK YOU!

the Jon Block Group
JONBLOCKGROUP.COM

## Disclosure

Any unmarked topic will be considered a "Yes"

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
| 1. | Salary or payments such as consulting fees or honoraria in excess of $10,000. | X | |
| 2. | Equity interests such as stocks, stock options or other ownership interests. | X | |
| 3. | Status or position as an officer, board member, trustee, owner. | | |
| 4. | Loan or intellectual property rights. | | |
| 5. | Research funding. | | |
| 6. | Any other relationship, including travel arrangements. | X | |

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

DePuy Synthes Mitek Sports Medicine, A Johnson & Johnson Company.

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
| 7. | Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government). | X | |

If yes to #7, provide name and funding Sources:

DePuy Synthes Mitek Sports Medicine, A Johnson & Johnson Company

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X _____ 10,23,13 Samir Bhattacharyya

*Signature* *Date* *Print Name*

**For questions contact:** Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126

# *Do Hyaluronic Acid Injections Postpone Total Knee Replacement?*

**November 2013**

DePuy Synthes
MITEK SPORTS MEDICINE
COMPANIES OF Johnson & Johnson
People inspired™

## Introduction and Objective

- More than 27 million adults in the US have knee osteoarthritis (OA), a painful and life-altering disease
- Viscosupplementation with hyaluronic acid (HA) injections helps restore synovial fluid properties in the knee, leading to less pain and improved clinical outcomes
- Total knee replacement (TKR) usually is reserved as the final treatment option
- The present study examined the association of the use of HA injections in delaying TKR in patients with knee OA

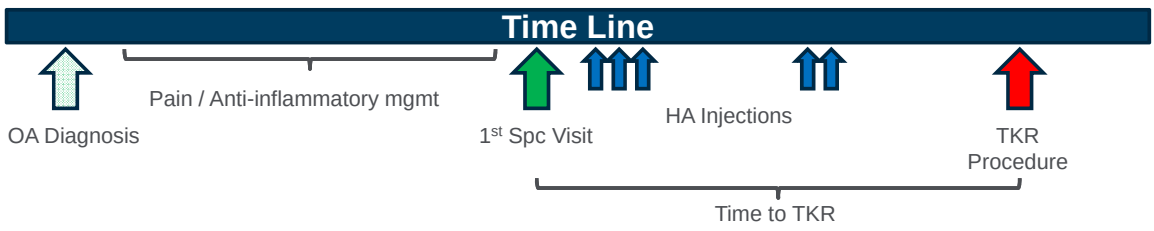
## Database

Retrospective analysis of administrative data using the Truven MarketScan Commercial and Medicare Supplemental Database

- Contains healthcare experience of several million individuals (annually).
- Contains healthcare information from multiple payors
- These individuals' healthcare is provided under a variety of fee-for-service (FFS), fully capitated, and partially capitated health plans, including preferred provider organizations, point-of-service plans, indemnity plans, and health maintenance organizations.

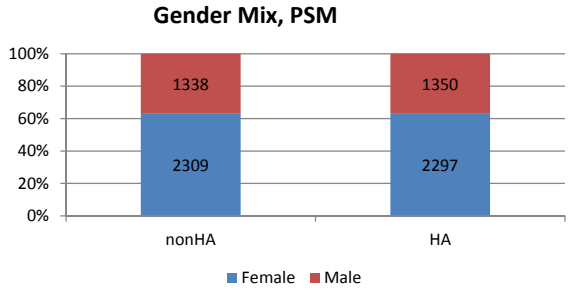
## Methods

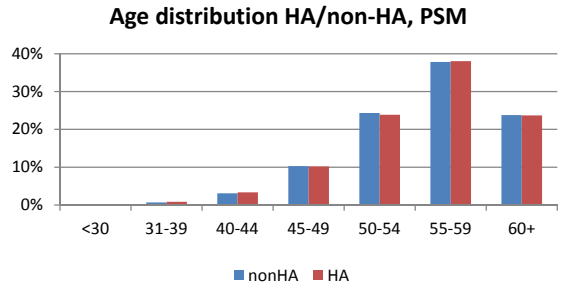
- Patients
  - Continuously enrolled from 1/1/2007 through 12/31/2011
  - Diagnosis of Knee OA **and** Total Knee Replacement
  - Patients under 18 excluded
  - Patients excluded if HA was administered after their TKR



# Analysis Design

**Propensity Score Matched (PSM) populations were used**



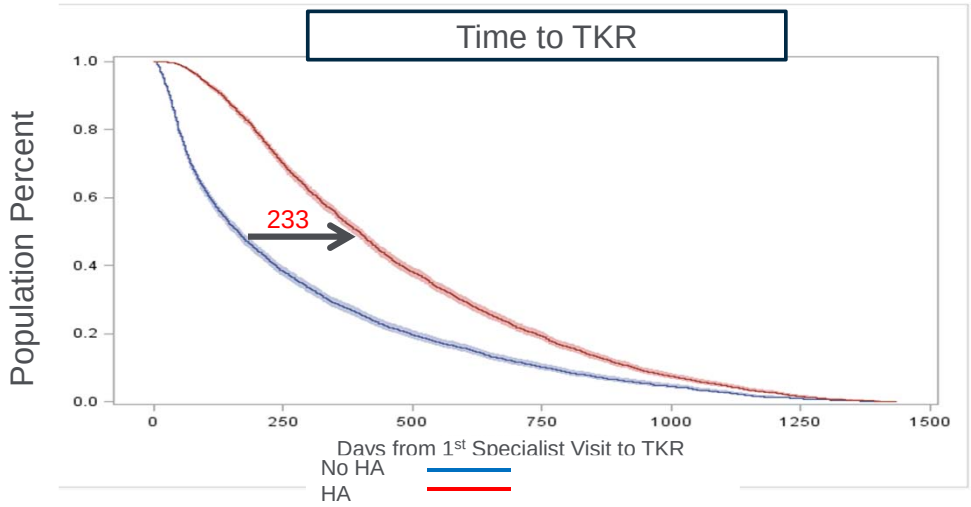




Of the 4,178 patients who received HA, **3,647** were successfully matched using the propensity scoring model factors*.

*Rosenbaum, PR: The central role of the propensity score in observational studies for causal effects. Biometrika (1983) 70 (1): 41-55.

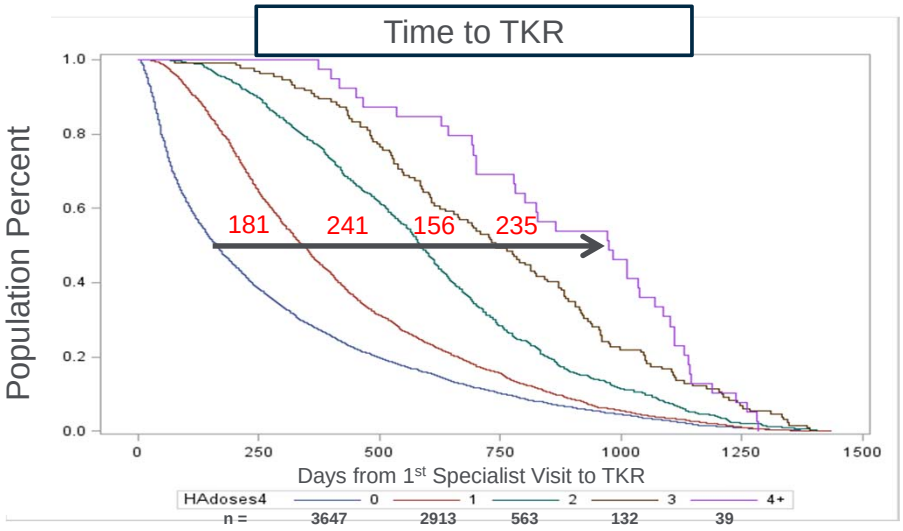
# Association between HA Use and Time to TKR

Patients who received HA injections waited **233 days longer** from their first specialist visit to get to their TKR than patients who did not receive HA



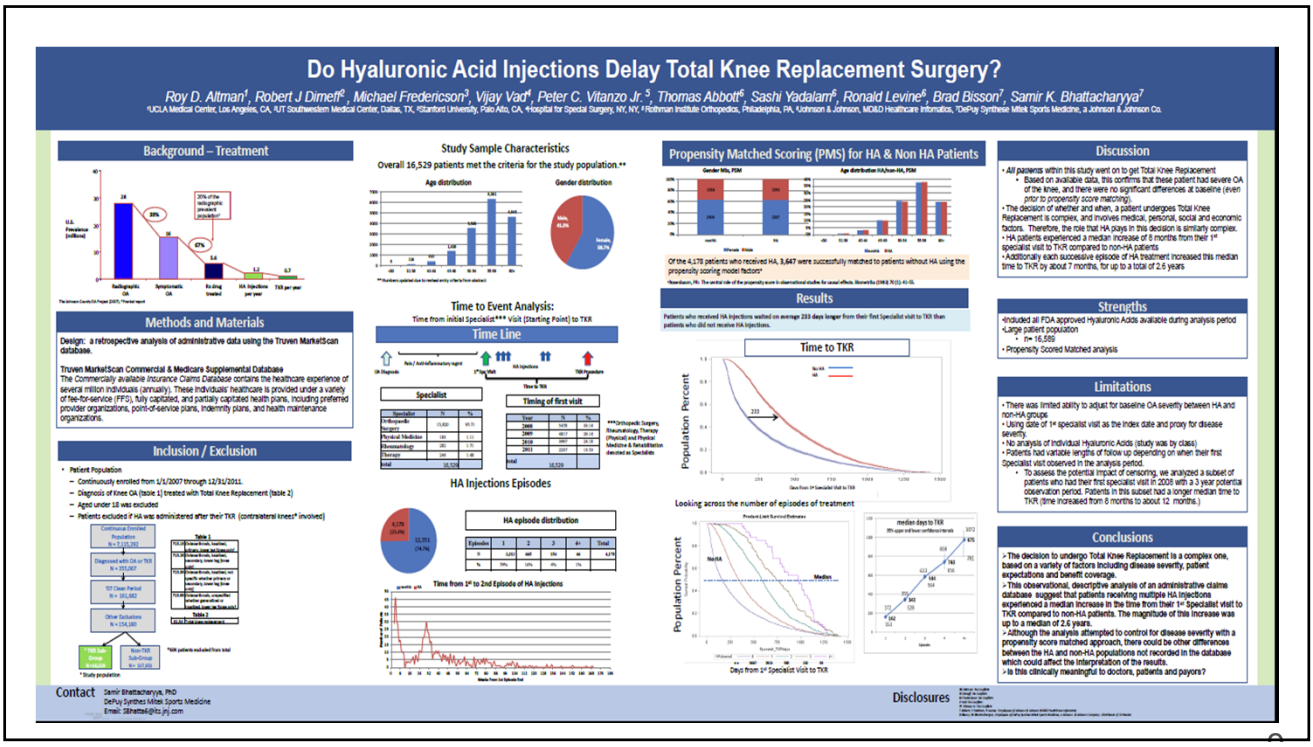
# Repeat Use of HA and Time to TKR

For each additional episode of treatment, patients waited on average 203 days longer to get their TKR; a very consistent "dose response"




# Discussion

- This observational, descriptive analysis of an administrative database provides data that suggest that patients receiving HA injections are able to postpone their TKR procedures from initial specialists visit by up to 2.6 years
- Robust patient population
- Propensity Matched Scored population limiting bias
- Although the analysis attempted to control for disease severity by propensity score matching, there could be remaining differences between the HA and non-HA populations not recorded in the database which could affect the interpretation of the results



# Do Hyaluronic Acid Injections Delay Total Knee Replacement Surgery?

Roy D. Altman[1], Robert J Dimeff[2], Michael Fredericson[3], Vijay Vad[4], Peter C. Vitanzo Jr.[5], Thomas Abbott[6], Sashi Yadalam[6], Ronald Levine[6], Brad Bisson[7], Samir K. Bhattacharyya[7]

[1]UCLA Medical Center, Los Angeles, CA, [2]UT Southwestern Medical Center, Dallas, TX, [3]Stanford University, Palo Alto, CA, [4]Hospital for Special Surgery, NY, NY, [5]Rothman Institute Orthopedics, Philadelphia, PA, [6]Johnson & Johnson, MD&D Healthcare Informatics, [7]DePuy Synthese Mitek Sports Medicine, a Johnson & Johnson Co.

## Background – Treatment

## Methods and Materials

Design: a retrospective analysis of administrative data using the Truven MarketScan database.

Truven MarketScan Commercial & Medicare Supplemental Database

The Commercially available Insurance Claims Database contains the healthcare experience of several million individuals (annually). These individuals' healthcare is provided under a variety of fee-for-service (FFS), fully capitated, and partially capitated health plans, including preferred provider organizations, point-of-service plans, indemnity plans, and health maintenance organizations.

## Inclusion / Exclusion

- Patient Population
  - Continuously enrolled from 1/1/2007 through 12/31/2011.
  - Diagnosis of Knee OA (table 1) treated with Total Knee Replacement (table 2)
  - Aged under 18 was excluded
  - Patients excluded if HA was administered after their TKR (contralateral knees* involved)

## Study Sample Characteristics

Overall 16,529 patients met the criteria for the study population.**

## Time to Event Analysis:

Time from initial Specialist*** Visit (Starting Point) to TKR

### Time Line

### Specialist

### Timing of first visit

***Orthopedic Surgery, Rheumatology, Therapy (Physical) and Physical Medicine & Rehabilitation detected as Specialists

## HA Injections Episodes

### HA episode distribution

| Episodes | 1 | 2 | 3 | 4+ | Total |
|---|---|---|---|---|---|
| N | 3,531 | 445 | 156 | 46 | 4,178 |
| % | 75% | 11% | 4% | 1% | |

### Time from 1st to 2nd Episode of HA Injections

## Propensity Matched Scoring (PMS) for HA & Non HA Patients

Of the 4,178 patients who received HA, 3,647 were successfully matched to patients without HA using the propensity scoring model factors*

## Results

Patients who received HA injections waited on average 233 days longer from their first Specialist visit to TKR than patients who did not receive HA injections.

### Time to TKR

Population Percent

### Looking across the number of episodes of treatment

Population Percent

Days from 1st Specialist Visit to TKR

## Discussion

- All patients within this study went on to get Total Knee Replacement
  - Based on available data, this confirms that these patient had severe OA of the knee, and there were no significant differences at baseline (even prior to propensity score matching).
- The decision of whether and when, a patient undergoes Total Knee Replacement is complex, and involves medical, personal, social and economic factors. Therefore, the role that HA plays in this decision is similarly complex.
- HA patients experienced a median increase of 8 months from their 1st specialist visit to TKR compared to non-HA patients
- Additionally each successive episode of HA treatment increased this median time to TKR by about 7 months, for up to a total of 2.6 years

## Strengths

- Included all FDA approved Hyaluronic Acids available during analysis period
- Large patient population
  - n= 16,599
- Propensity Scored Matched analysis

## Limitations

- There was limited ability to adjust for baseline OA severity between HA and non-HA groups
- Using date of 1st specialist visit as the index date and proxy for disease severity.
- No analysis of individual Hyaluronic Acids (study was by class)
- Patients had variable lengths of follow up depending on when their first Specialist visit observed in the analysis period.
  - To assess the potential impact of censoring, we analyzed a subset of patients who had their first specialist visit in 2010 with a 3 year potential observation period. Patients in this subset had a longer median time to TKR (time increased from 8 months to about 12 months.)

## Conclusions

- The decision to undergo Total Knee Replacement is a complex one, based on a variety of factors including disease severity, patient expectations and benefit coverage.
- This observational, descriptive analysis of an administrative claims database suggest that patients receiving multiple HA injections experienced a median increase in the time from their 1st Specialist visit to TKR compared to non-HA patients. The magnitude of this increase was up to a median of 2.6 years.
- Although the analysis attempted to control for disease severity with a propensity score matched approach, there could be other differences between the HA and non-HA populations not recorded in the database which could affect the interpretation of the results.
- Is this clinically meaningful to doctors, patients and payors?

Contact Samir Bhattacharyya, PhD
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Disclosures

Council 28 AFSCME
Washington Federation of State Employees

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November 7, 2013

Dorothy Frost Teeter, Director
Washington State Health Care Authority
626 8th Avenue SE
P.O. Box 45502
Olympia, WA 98504-5502

Director Teeter:

It has been brought to the attention of the Washington Federation of State Employees (WFSE) that the Health Technology Clinical Committee will be reviewing viscosupplementation at the upcoming November 15th meeting.

As you well know, the PEBB recently expanded UMP eligibility criteria for bariatric surgery to bring the plan's coverage up to national standards and match what the other state plans offer. If viscosupplementation is removed as a covered benefit from the UMP, it is a loss of benefits to the bulk of our members, and creates a new disparity not only between the state-offered plans, but with other major insurance plans. Based on an informal review of benefit plans offered in Washington State, we found that all plans cover viscosupplementation with conditions. Should viscosupplementation coverage be eliminated for UMP, it would make the UMP an outlier.

Clearly, the WFSE is not a clinical expert, but we are very concerned that the state is the only insurer in Washington that feels there is new creditable evidence to change time-tested coverage policies for this technology. There is no new evidence we're aware of that changes the efficacy or safety of this technology. It appears that the most significant new evidence is the change in the American Academy of Orthopaedic Surgeons Treatment Guidelines wherein viscosupplementaion is no longer recognized as an effective treatment for osteoarthritis of the knee. While this recommendation is based on best practices, "expert opinion," is not a highly-rated evidence source. Additionally, it could be argued that such a position by the Orthopaedic Surgeons is not impartial and unbiased.

The WFSE believes that it would be unfair and inconsistent for its members receiving care on a fee-for-service basis not to have appropriate access to viscosupplementation. The Federation believes that treatments should be consistently covered by both the fee-for-service and managed care health plans.

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Respectfully,

Greg Devereux
Executive Director
WA Federation of State Employees

CC: Josh Morse (josh.morse@hca.wa.gov)
Jason McGill (jason.mcgill@gov.wa.gov)

Washington State Health Care Authority
Health Technology Assessment

# Agency Medical Director Comments

## Hyaluronic Acid Injections for Knee Osteoarthritis, Re-Review

Robert D. Mootz, DC
Associate Medical Director
Department of Labor & Industries
November 15, 2013

### HA Injections for Knee OA: Background

- **OA of the Knee**
  - Affects up to 12% of older adults.
  - Involves damage to articular cartilage, subchondral bone changes and may be painful.
  - Usual care: PT, OT, assistive devices, NSAIDS, analgesics.
  - Refractory Care: Steroids, aspiration
- **Issues**
  - NSAIDs are effective for OA however prolonged use may have serious GI effects. Steroid injections may worsen joint long term.
- **Intra Articular HA Injection**
  - AKA, viscosupplementation
  - Thought to assist lubrication and improve cartilage repair
- **FDA Approval**
  - As a device, not a drug.

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## Agency Concerns

**2010**

- **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

**2013**

- **Safety (Medium)**
  - Adverse event concerns persist
- **Efficacy (Medium)**
  - New studies available
- **Cost (Medium)**
  - Recent agency experience may attenuate some concerns



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HA Injections for Knee OA

## 2010 Decision – Covered With Conditions

**For treatment of pain associated with osteoarthritis (OA) of the knee when all of the following conditions are met:**

•In patients who have not had an adequate response to non-pharmacological conservative treatment and simple analgesics;

•Is limited to two courses per year with at least four months between courses;

•Documented evidence of clinical benefit from the prior course of treatment is required for subsequent treatment courses.

**Non-covered for other indications**

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## Safety Issues

- Localized adverse effects appear to be more common than with comparators (e.g., placebo, saline).
- Serious adverse events such as pseudosepsis are rare but usually can be resolved.







## Effectiveness Issues

- Statistically measurable improvements in pain and function reported in placebo trials. Clinical significance is questionable.
- Larger, better designed trials show smaller effects that are clinically insignificant.
- Benefit may be greater in less severe cases and individuals under age 65.
- Evidence suggests there is no effect on quality of life.
- Viscosupplementation (VS) may provide longer lasting benefit than steroids.
- There is inadequate evidence comparing VS to glucosamine/chondroitin or conservative measures such as exercise.

HA Injections for Knee OA

## Cost Issues

- Agency experience suggests a rapid initial growth that has leveled off.
- There may be tradeoffs:
  - Some products may cost less per course, but may have increased risk for side effects when multiple doses are required.
- Published studies are of variable methodology and mixed conclusions.

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Health Technology Assessment

HA Injections for Knee OA: Billing Codes

## Codes and CMS Hyaluronic Injectables Pricing

| HCPCS | Description | Price Basis | Medicare Price | Dosing /Injection Counts | Per Dose* | Treatment Cost* |
|---|---|---|---|---|---|---|
| J7321 | Hyalgan/Supartz inj per dose | per dose | 85.133 | 2 mL, 5 doses | 85.133 | $425.65 |
| J7323 | Euflexxa inj/dose | per dose | 152.880 | 2 mL, 3 doses | 152.880 | $458.64 |
| J7324 | Orthovisc inj per dose | per dose | 172.197 | 2 mL, 3 doses | 172.197 | $516.60 |
| J7325 | Synvisc | 1 MG (8mg/mL) | 12.570 | 2 mL, 3 doses | 201.12 | $603.36 |
| | Synvisc-One | 1 MG (8mg/mL) | 12.570 | 6 mL/dose, 1 dose | 603.36 | $603.36 |
| J7326 | Gel-One | per dose | 620.104 | 3 mL, 1 dose | 620.10 | $620.10 |

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Health Technology Assessment

HA Injections for Knee OA

## PEBB Utilization

| Agency/Year | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 7 -Yr Total |
|---|---|---|---|---|---|---|---|---|
| **PEBB Avg Annual Members** | **160K** | **172K** | **205K** | **211K** | **213K** | **213K** | **213K** | |
| **All PEBB HA Patients** | **977** | **916** | **1183** | **1186** | **1327** | **1481** | **1517** | |
| **PEBB Paid/Knee OA HA** | $250K | $353K | $598K | $628K | $643K | $620K | $669K | $3.8M |
| Avg Paid /Procedure | $139 | $131 | $152 | $152 | $169 | $161 | $174 | $156 |
| Avg Paid, Primary | | | | $257 | $270 | $275 | $309 | $277 |
| PEBB Primary % of Inj. | | | | 45.6% | 49.7% | 45.8% | 45.6% | 30.3% |
| Knee OA HA Patients | 790 | 674 | 946 | 978 | 1063 | 1226 | 1290 | |
| Knee OA HA Injections | 1797 | 2695 | 3932 | 4937 | 4594 | 4359 | 4372 | 26,686 |
| Average Inj per patient | 2.3 | 4 | 4.2 | 5 | 4.3 | 3.6 | 3.4 | |
| Average Inj courses/pt | | | | 1.6 | 1.6 | 1.5 | 1.5 | |
| **PEBB Comparator Counts** | | | | | | | | |
| Knee OA Diagnosis Pts | | 3929 | 5174 | 5602 | 5906 | 6179 | 6472 | |
| Knee Arthroplasty Pts | | 543 | 674 | 772 | 837 | 834 | 885 | |

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HA Injections for Knee OA

## Medicare Utilization

| Agency/Year | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 7 Yr Total |
|---|---|---|---|---|---|---|---|---|
| **Medicaid Avg Annual Pts** | | 379K | 393K | 417K | 424K | 435K | 478K | |
| **All Medicaid HA Patients** | **196** | **320** | **511** | **860** | **1081** | **1265** | **1265** | |
| **Medicaid Paid/Knee OA HA** | $97K | $149K | $216K | $278K | $284K | $398K | $378K | $1.8M |
| Avg Paid /Procedure | $196 | $173 | $151 | $165 | $93 | $104 | $100 | $119 |
| Avg Paid, Primary | | | | $188 | $205 | $240 | $254 | $214 |
| Non-Mcare % of Inj. | | | | 51.0% | 30.7% | 32.3% | 28.2% | 33.2% |
| Knee OA HA Patients | 167 | 275 | 437 | 690 | 941 | 1104 | 1124 | |
| Knee OA HA Injections | 494 | 860 | 1426 | 1682 | 3042 | 3843 | 3782 | 15,129 |
| Average Inj per patient | 3 | 3.1 | 3.3 | 2.4 | 3.2 | 3.5 | 3.4 | |
| Average Inj courses/pt | | | | 1.2 | 1.1 | 1.2 | 1.2 | |
| **Medicaid Comparator Counts** | | | | | | | | |
| Knee OA Diagnosis Pts | | | | 9714 | 10770 | 11447 | 10866 | |
| Knee Arthroplasty Pts | | | | 564 | 616 | 646 | 529 | |

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HA Injections for Knee OA

## L & I Utilization

| Agency/Year | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 7-Yr Total |
|---|---|---|---|---|---|---|---|---|
| **L&I Avg Annual Patients** | **163K** | **156K** | **147K** | **126K** | **123K** | **121K** | **122K** | |
| **All L&I HA Patients** | **214** | **509** | **479** | **504** | **508** | **488** | **433** | |
| **L&I Paid/Knee OA HA** | $133K | $340K | $377K | $302K | $308K | $307K | $270K | $2.04M |
| Knee OA HA Patients | 154 | 364 | 438 | 351 | 352 | 321 | 262 | |
| Knee OA HA Injections | 395 | 1136 | 1303 | 1131 | 992 | 954 | 868 | 6,779 |
| Average Inj per patient | 2.6 | 3.1 | 3 | 3.2 | 2.8 | 3 | 3.3 | |
| Average Inj courses/pt | | | | 1.1 | 1.1 | 1.1 | 1.3 | |
| **L&I Comparator Counts** | | | | | | | | |
| Knee OA Diagnosis Pts | 7888 | 8387 | 8578 | 8028 | 7375 | 7168 | 7209 | |
| Knee Arthroplasty Pts | 242 | 281 | 328 | 362 | 355 | 366 | 314 | |

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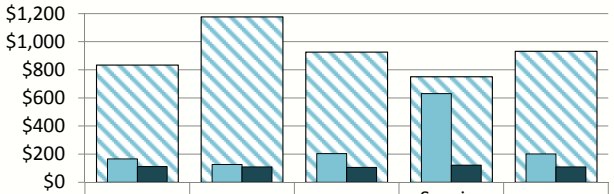
HA Injections for Knee OA:
Other Agencies Similar

## PEBB Utilization Example

**PEBB Primary Avg Injection Course Allowed $ by Product, 2009-2012**




| | Euflexxa | Hyalgan | Orthovisc | Synvisc One | Synvisc |
|---|---|---|---|---|---|
| Injection Course | $834 | $1,177 | $926 | $751 | $932 |
| Injectable Material | $166 | $126 | $203 | $630 | $201 |
| Professional Fee | $111 | $109 | $106 | $121 | $110 |
| Inj Count/Course | 3 | 5 | 3 | 1 | 3 |
| % Total Allowed $ | 12.4% | 7.8% | 8.4% | 12.3% | 7.1% |

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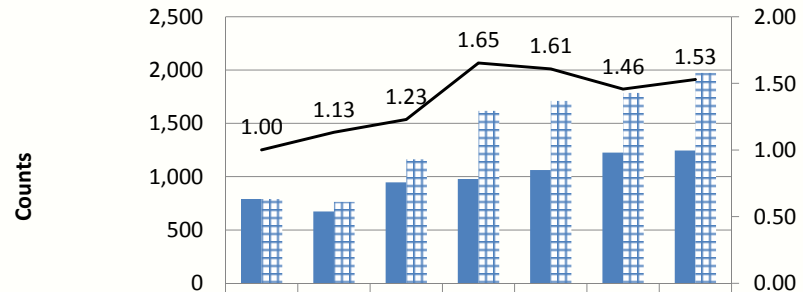
HA Injections for Knee OA:
Other Agencies Similar

## PEBB Experience Example

**PEBB Injection Courses per Patient 2006-2012**




| | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|
| Patients | 790 | 674 | 946 | 978 | 1063 | 1226 | 1245 |
| Treatment Courses | 791 | 764 | 1163 | 1617 | 1710 | 1786 | 1973 |
| Avg Tx per Patient | 1.00 | 1.13 | 1.23 | 1.65 | 1.61 | 1.46 | 1.53 |

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HA Injections for Knee OA

## Coverage Decisions

- NICE 2008 recommended against
  - Emphasized small effect size and cost
- Oregon Health Evidence Review Committee 2012
  - Non-coverage due to insignificant clinical effects

## Guidelines less positive since 2010

- AAOS (2013) did not recommend HA *(strong)*
  - 2010 Did not recommend for or against
  - 2013 Based on original studies; Considered MCID = 0.39
- ACR (2012) made no recommendations for HA
  - 2000 recommendation similar to HTCC (recommend for inadequate response to other treatment)

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**HA Injections for Knee OA: Agency Considerations**

- Based on reasonable level of MCID, evidence does not show superiority to placebo/sham; type of product; cost; or number of injections.
- Additional evidence since 2010 demonstrates lack of efficacy.
- Persistent evidence suggesting adverse events are a concern.
- Products requiring multiple injections per course may slightly increase risk for adverse events.
- Professional societies have tightened guidelines or recommended against use since 2010.
- Other well done evidence-based coverage reviews have made non-coverage decisions based on this evidence.

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**HA Injections for Knee OA: Agency Recommendations**

## Consider making non-coverage determination

- Meaningful clinical effect on pain still not demonstrated; little evidence on other patient outcomes.
- Harms occur, usually minor, but include serious adverse events (pseudosepsis).

If HTCC finds evidence suggestive of net health benefit, continue coverage conditions including:

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

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## Questions?

More Information:
http://www.hca.wa.gov/hta/Pages/hyaluronic_visco.aspx

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## Supplemental Information

**HA Product Information**

- Orthovisc ® is a registered trademark of DePuy Mitek, Inc., a Johnson&Johnson company.
- Synvisc and Synvisc 1 are trademarks of Genzyme Corporation.
- Hyalgan® is a registered trademark of Sanofi-Synthelabo.
- Supartz® is a registered trademark of Seikagaku Corporation.
- Euflexxa™ is a trademark of Ferring Pharmaceuticals, Inc.
- GEL-ONE ® is a registered trademark of Zimmer, Inc.
(FDA approved for use 12/2012: minor component of agency data).

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| Related Medical Codes | | |
|---|---|---|
| | 20610 | Arthrocentesis, aspiration and/or injection, major joint or bursa, evaluation and management |
| 2006 | J7320 | Hylan G-F 20, 16 mg for intra-articular injection [i.e., Synvisc] |
| | J7317 | Sodium hyaluronate, per 20 to 25 mg dose for intra-articular injection [i.e., Hyalgan or Supartz] |
| 2007 | Q4083 | Hyaluronan or derivative, Hyalgan or Supartz, for intra-articular injection, per dose |
| | Q4084 | Hyaluronan or derivative, Synvisc, for intra-articular inj, per dose |
| | Q4085 | Hyaluronan or derivative, Euflexxa, for intra-articular inj, per dose |
| | Q4086 | Hyaluronan or derivative, Orthovisc, for intra-articular inj, per dose |
| 2008 | J7321 | Hyaluronan or derivative, Hyalgan or Supartz, for intra-articular injection, per dose |
| | J7322 | Hyaluronan or derivative, Synvisc, for intra-articular inj, per dose |
| | J7323 | Hyaluronan or derivative, Euflexxa, for intra-articular inj, per dose |
| | J7324 | Hyaluronan or derivative, Orthovisc, for intra-articular inj, per dose |
| 2010 | J7325 | Synvisc and Synvisc-1 (single injection tx) |
| 2012 | J7326 | Gel-One Cross-linked Hyaluronate, Zimmer |

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# Hyaluronic Acid/ Viscosupplementation

**Clinical Expert**

Howard Alan Chansky, MD

Professor & Vice-Chair, Orthopaedics and Sports Medicine, University of Washington
Chief, Section of Orthopaedics, VA Puget Sound Health Care System
Chief, Orthopaedics and Sports Medicine, University of Washington Medical Center

## Disclosure

Any unmarked topic will be considered a "Yes"

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
| 1. | Salary or payments such as consulting fees or honoraria in excess of $10,000. | | ✓ |
| 2. | Equity interests such as stocks, stock options or other ownership interests. | | ✓ |
| 3. | Status or position as an officer, board member, trustee, owner. | | ✓ |
| 4. | Loan or intellectual property rights. | | ✓ |
| 5. | Research funding. | | ✓ |
| 6. | Any other relationship, including travel arrangements. | | ✓ |

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

| | Potential Conflict Type | Yes | No |
|---|---|---|---|
| 7. | Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government). | | ✓ |

If yes to #7, provide name and funding Sources:

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X [signature] 11/4/13 Howard Chansky

*Signature* *Date* *Print Name*

**For questions contact:** Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126

# CURRICULUM VITAE

## Howard Alan Chansky, MD

**Professor & Vice-Chair, Orthopaedics and Sports Medicine**
**University of Washington**

**Chief, Section of Orthopaedics, VA Puget Sound Health Care System**
**Chief, Orthopaedics and Sports Medicine, University of Washington Medical Center**

1660 South Columbian Way S-112-ORT
Seattle, Washington 98108
(206) 764-2215 – Office
(206) 764-2529 – Fax
chansky@u.washington.edu

**PERSONAL DATA**

| | |
|---|---|
| Birth**:** | May 10, 1960; Boston, MA |
| Citizenship: | U.S.A. |

**EDUCATION**

| | |
|---|---|
| May 1982 | B.S. Degree (Electrical Engineering)<br>Cornell University, Ithaca, NY |
| May 1987 | M.D. Degree<br>University of Pennsylvania School of Medicine,<br>Philadelphia, PA |

**POSTGRADUATE TRAINING**

| | |
|---|---|
| June 1987 - June 1988 | Internship—Department of General Surgery<br>The Hospital of The University of Pennsylvania<br>Philadelphia, PA |
| June 1988 - June 1992 | Residency—Department of Orthopaedic Surgery<br>The Hospital of The University of Pennsylvania<br>Philadelphia, PA |
| Aug. 1992 - Aug. 1994 | Acting Instructor—Orthopaedic Oncology<br>Department of Orthopedics<br>University of Washington, Seattle, WA |

**FACULTY POSITIONS**

| | |
|---|---|
| 1988 – 1992 | Assistant Instructor, Department of Orthopaedic Surgery<br>The Hospital of The University of Pennsylvania,<br>Philadelphia, PA |
| Aug. 1992 - Feb. 1996 | Acting Instructor, Department of Orthopaedics<br>University of Washington Medical Center and the Children's<br>Hospital & Medical Center, Seattle, WA |
| Aug. 1993 - Feb. 1996 | Acting Instructor, Department of Orthopaedics<br>Attending Physician and Research Fellow |

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|---|---|
| | VA Puget Sound Health Care System, Seattle, WA |
| Feb. 1996 – Jun. 2002 | Assistant Professor, Department of Orthopaedics & Sports Medicine, University of Washington School of Medicine, Seattle, WA |
| January 2001 – Present | Associate Medical Staff, Seattle Cancer Care Alliance, Seattle, WA |
| July 2002 – June 2005 | Associate Professor, Department of Orthopaedics & Sports Medicine, University of Washington School of Medicine, Seattle, WA |
| June 2004 – Present | Vice Chair, Department of Orthopaedics & Sports Medicine, University of Washington School of Medicine, Seattle, WA |
| Sept 2004 –Aug 2005 | Senator, Faculty Senate, University of Washington, Seattle, WA |
| July 2005 – Present | Professor, Department of Orthopaedics & Sports Medicine, University of Washington School of Medicine, Seattle, WA |

**HOSPITAL POSITIONS**

| | |
|---|---|
| Feb. 1993 - Present | Staff Orthopaedic Surgeon<br>VA Puget Sound Health Care System, Seattle, WA |
| Feb. 1993 - Present | Staff Orthopaedic Surgeon<br>University of Washington Medical Center, Seattle, WA |
| Feb. 1996 – Present | Staff Orthopaedic Surgeon<br>Harborview Medical Center, Seattle, WA |
| Feb. 1996 - Present | Courtesy Staff<br>Children's Hospital & Medical Center, Seattle, WA |
| Mar. 1999 - Present | Chief, Section of Orthopaedics<br>VA Puget Sound Health Care System, Seattle, WA |
| Feb. 2010 – Present | Chief, Orthopaedics and Sports Medicine<br>University of Washington Medical Center |

**HONORS**

| | |
|---|---|
| 1978 - 1982 | Dean's List, eight out of eight semesters at Cornell University |
| 1981 | Eta Kappa Nu Electrical Engineering Honor Society |
| 1981 | Tau Beta Pi Engineering Honor Society |
| 1981 | Vice President of Psi Upsilon Fraternity |
| 1982 | Senior Kodak Award for Academic Excellence (one of the top five graduates in the School of Electrical Engineering) |

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|---|---|
| 1982 | B.S.E.E. with "Distinction" from Cornell University |
| 1987 | M.D. in the "Outstanding" Category from the University of Pennsylvania |
| 1995 | "New Investigator Recognition Award," Orthopaedic Research Society |
| June 1996 | "Academic Faculty Teaching Award," University of Washington, Department of Orthopaedics & Sports Medicine |
| 2004 | Musculoskeletal Transplant Foundation / OREF Herndon Research Residency Awards: Splicing Factors Effect Chondrocyte Differentiation and Collagen Synthesis, Principal Investigator (Resident Principal Investigator: Eric Klineberg, M.D.) |
| June 2004 | "Academic Faculty Teaching Award," University of Washington, Department of Orthopaedics & Sports Medicine |
| 2004 | Accepted into membership by the American Orthopaedic Association |
| 2006 – 2012 | Checkbook.org Top Doctor |
| 2011 | UWMC Service Award |
| 2011 - 2012 | US News and World Report Top Doctor |

**BOARD CERTIFICATION**

American Board of Orthopaedic Surgery Part I (written)—Passed July 1992
Part II (oral)—Passed July 1995
Recertified—April 2004

**CURRENT LICENSE TO PRACTICE**

| | |
|---|---|
| State of Washington | Washington State Physician and Surgeon, 1992<br>Medical License No. 29712 (active) |
| State of Pennsylvania | Pennsylvania Medical Physician and Surgeon**,** 1989<br>Medical License No. 43161E (inactive) |

**PROFESSIONAL ORGANIZATIONS**

| | |
|---|---|
| 1995 - Present | Member, American Board of Orthopaedic Surgery |
| 1995 - Present | Member, Orthopaedic Research Society |
| 1995 - Present | Member, American Medical Association |
| 1997 - Present | Member, American Academy of Orthopaedic Surgeons |
| 2004 - Present | Member, American Orthopaedic Association |

**TEACHING RESPONSIBILITIES**

A. RESPONSIBILITY FOR COURSES

| | |
|---|---|
| 1993 – Present | Orthopaedic Pathology Review Course<br>Children's Hospital & Regional Medical Center |
| 1995 – Present | Supervisor, Orthopaedic Residency Rotation at the Puget Sound Veterans Administration Medical Center, Seattle, WA |
| 1997 – Present | Career Counselor, Medical Student Career Counseling<br>University of Washington School of Medicine, Seattle, WA |
| 1998 – Present | Preceptor for MEDEX Physician Assistant Program<br>University of Washington School of Medicine, Seattle, WA |
| Dec. 1999 – Feb. 2000 | Instructor, Problem Based Learning, Multidisciplinary PBL Component, University of Washington School of Medicine, Seattle, WA |
| January 2000 – Present | Director, Orthopaedic Resident Workshop (Ortho "Boot Camp")<br>Department of Orthopaedics, University of Washington, Seattle, WA |
| Dec. 2000 – Feb. 2001 | Instructor, Problem Based Learning, Multidisciplinary PBL Component, University of Washington School of Medicine, Seattle, WA |
| Dec. 2001 – Feb. 2002 | Instructor, Problem Based Learning, Multidisciplinary PBL Component, University of Washington School of Medicine, Seattle, WA |
| May 2004 | Career Counselor, Residency Selection Forum, University of Washington School of Medicine |

B. SPONSORSHIPS

| | |
|---|---|
| 1998 – 2001 | Faculty Sponsor for Resident Research, Resident: Matt Camuso, MD. Project title: "Supraphysiologic Testosterone Administration in Elderly Men Undergoing Total Joint Replacement and Fixation of Hip Fracture", University of Washington School of Medicine, Seattle, WA |
| March 1999 – March 2000 | Sponsor for Medical Student Research Training Program. Medical Student: David Woods. Project title: "Supraphysiologic Testosterone Administration in Elderly Men Undergoing Operation Fixation of Hip Fracture." Award: $2,000, University of Washington School of Medicine, Seattle, WA |
| January 2000 – 2002 | Faculty Sponsor for Resident Research, Resident: Tim Rapp, MD, Project 1: "Clonality of Chondroid Tumors," Project 2: "Oncogenic Fusion Protein TLS/CHOP Interferes with RNA Splicing," University of Washington School of Medicine, Seattle, WA |

| | |
|---|---|
| July 2000 – 2001 | Faculty Sponsor for Medical Student Research: Student: Jeremiah Clinton, Project: Cloning and Sequencing of the TLS-Associated Splicing Factors TASR-1 and TASR-2, University of Washington School of Medicine, Seattle, WA |
| April 2001 – 2002 | Faculty Sponsor for Medical Student Research, ISMS and MSRTP, Student: David Odell, Project: Alternative Splicing and Fusion Proteins in Ewing's sarcoma, University of Washington School of Medicine, Seattle, WA |
| 2003 – 2005 | Faculty Sponsor for Medical Student Research. Student: Waqqar Khan-Farooqi, Project: RNA interference to inhibit EWS/FLI-1 Ewing's sarcoma fusion protein, University of Washington School of Medicine, Seattle, WA |
| 2003 – 2006 | Faculty Sponsor for Medical Student Research. Student: Burt Yaszay, Project: DNA microarray analysis of Ewing's sarcoma cell lines treated with short-interfering RNAs, University of Washington School of Medicine, Seattle, WA |
| 2003 – 2006 | Faculty Sponsor for Medical Student Research. Student: Eric Klineberg, Project: Splicing Factors Effect Chondrocyte Differentiation and Collagen Synthesis, University of Washington School of Medicine, Seattle, WA |
| 2004 – 2005 | Faculty Sponsor for Medical Student Research. Student: Allison MacLennan, Project: The role of DKKI in the genesis of Ewing's sarcoma, University of Washington School of Medicine, Seattle, WA |
| 2004 – 2005 | Faculty Sponsor for Medical Student Research. Student: Evan Ellis, Project: Biomechanical analysis of patella tracking with subvastus versus standard approach in total knee arthroplasty, University of Washington School of Medicine, Seattle, WA |
| 2006 – 2007 | Faculty Sponsor for Medical Student Research. Student: Jason Wilcox, Project: Silencing of EWS/FLI1 expression by lentivirus-mediated RNAi,University of Washington School of Medicine, Seattle, WA |
| 2008 – 2009 | Faculty Sponsor for Medical Student Research. Student: Dustin Sepich, Project: Hip fracture outcomes in the Seattle Veterans Health Administration, University of Washington School of Medicine, Seattle, WA |

C. PRESENTATIONS AND LECTURES

| | |
|---|---|
| December 1992 | The Surgical Treatment of Fibrous Dysplasia, Department of Orthopaedics Grand Rounds, Brown University |
| June 1993 - present | Musculoskeletal Pathology Review Course, Children's Hospital & Medical Center, Seattle, WA |

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|---|---|
| 1993 - present | Orthopaedic Resident Workshop, Orthopaedic Tumors and Infections |
| August 1993- present | Resident Lecture Series, University of Washington Department of Orthopaedics: Musculoskeletal Oncology (monthly) |
| October 1993 | American Foot and Ankle Society Review Course: Tumors of the Foot and Ankle, Seattle, WA |
| April 1995 | Grand Rounds, University of Washington Department of Orthopaedics: Biological and Clinical Aspects of Cartilage Transplantation |
| September 1995 | Resident Lecture Series, University of Washington Department of Orthopaedics: Molecular Biology for Orthopaedic Surgeons |
| June 1996 | Grand Rounds, University of Washington Department of Orthopaedics: The Science and Treatment of Osteomyelitis |
| February 1997 | Grand Rounds, University of Washington Department of Orthopaedics: Skeletal Metastases: Diagnosis and Treatment |
| March 1997 | Grand Rounds, University of Washington, VA Puget Sound Health Care System, Seattle Division, Department of Medicine: Infectious Arthritis, The Orthopaedic Perspective |
| July 1997 | National Kidney Cancer Association Annual Convention: Modern Multidisciplinary Treatment of Metastatic Bone Disease, SeaTac, WA |
| August 2000 | Multidisciplinary Oncology Conference, University of Washington, Department of Radiation Oncology: Multidisciplinary Prophylaxis and Treatment of Metastatic Bone Disease |
| November 2000 | Multidisciplinary Oncology Conference, University of Washington, VA Puget Sound Health Care System: Metastatic Bone Disease--The Orthopaedic Perspective |
| February 2001 | Grand Rounds, University of Washington Department of Orthopaedics and Sports Medicine, Assisted Scott Hacker MD in preparation of presentation on biology of cartilage injury and reconstruction |
| April 2001 | Pacific Crest School: What is the life of a doctor really like? |
| April 2002 | Sarcoma Meeting, Osaka University, Osaka, Japan, |
| June 2004 | Grand Rounds, University of Washington Department of Rheumatology: Orthopaedic Controversies and the Limits of Current Technology |

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|---|---|
| September 2004 | Lower Extremity Assessment of Adults Workshop, 27th Annual National Conference: Advanced Practice in Primary and Acute Care, University of Washington School of Nursing, Washington State Convention & Trade Center, Seattle, WA, |
| September 2004 | RNA Interference Workshop: Target Validation and Potential Therapeutic Applications For Childhood Cancer. Cancer Therapy Evaluation Program National Cancer Institute and NIH Office of Rare Diseases and Children's Oncology Group, Arlington, Virginia |
| January 2005 | Grand Rounds, University of Washington Department of Rheumatology: Ewing's Sarcoma--Sarcoma Fusion Proteins and RNA Interference |
| September 2006 | Arkansas Cancer Research Center's Forum, University of Arkansas for Medical Sciences: The Role of Cellular Senescence and pRB in the Biology of Ewing's Sarcoma |
| October 2006 | Margo Johnson Pathology Review Course, Department of Orthopaedics & Sports Medicine, University of Washington: The Role of Cellular Senescence and pRB in the Biology of Ewing's Sarcoma |
| September 2008 | Molecular Biology and Therapeutics in Musculoskeletal Oncology Research Symposium, American Academy of Orthopaedic Surgeons/Orthopaedic Research Society: EWS/Fli-1 and Cell Cycle Dysregulation. Salt Lake City, Utah |
| September 2009 | Chief of Medicine Conference, VA Puget Sound Health Care System: Septic Arthritis: the Surgical Perspective |
| October 2009 | Margo Johnson Pathology Review Course, Department of Orthopaedics & Sports Medicine, University of Washington: Paget's Disease: Orthopedic Implications |
| October 2010 | Margo Johnson Pathology Review Course, Department of Orthopaedics & Sports Medicine, University of Washington: Paget's Disease: Orthopedic Implications |
| October 2010 | Visiting Professor, Dartmouth Hitchcock Medical Center Senior Residents' Day. Molecular biology and animal models of Ewing's sarcoma |
| September 2011 | Harkins Resident Education Symposium, University of Washington: Surgical management of extremity sarcoma |
| October 2011 | Margo Johnson Pathology Review Course, Department of Orthopaedics & Sports Medicine, University of Washington: Paget's Disease: Orthopedic Implications |

D. INVITED KNOWLEDGEBASE ENTRIES

| | |
|---|---|
| July 2000 | **Chansky HA**, Raskind WH: Hereditary multiple exostoses. *Gene Clinics: Medical Genetics Knowledge Base* [database online], www.geneclinics.org |
| July 2003 | **Chansky HA**, Raskind WH: Hereditary multiple exostoses. *Gene Clinics: Medical Genetics Knowledge Base* [database online], www.geneclinics.org |
| September 2008 | Schmale, GA, Wuyts, W, **Chansky HA**, Raskind WH: Hereditary multiple osteochondromas. *Gene Clinics: Medical Genetics Knowledge Base* [database online], www.geneclinics.org |

**EDITORIAL RESPONSIBILITIES**

| | |
|---|---|
| 1996 - present | Ad hoc reviewer, *Journal of Orthopaedic Research* |
| 2001 - present | Ad hoc reviewer, *International Journal of Cancer* |
| 2001 - present | Section Medical Editor, Orthopedic Oncology, e-Medicine Online, www.eMedicine.com |
| 2004 – present | Ad hoc reviewer, *Cellular and Molecular Life Sciences* |
| 2004 - present | Ad hoc reviewer, *Clinical Orthopaedics & Related Research* |
| 2005 – present | Ad hoc reviewer, *University of Pennsylvania Orthopaedic Journal* |
| 2005 – present | Ad hoc reviewer, *European Journal of Human Genetics* |

**SPECIAL LOCAL RESPONSIBILITIES**

| | |
|---|---|
| 1993 - 2005 | Surgical Quality Insurance Committee, VA Puget Sound Health Care System, Seattle, WA |
| 1993 - 2004 | Infection Control Committee, VA Puget Sound Health Care System, Seattle, WA |
| 1993 - Present | Chair, Same Day Surgery Clinical Pathway Committee, VA Puget Sound Health Care System, Seattle, WA |
| Oct. 22 - 23, 1996 | VA Puget Sound Health Care System Leadership Conference, Tacoma, WA |
| 1997 - 2010 | Medical Director, Same Day Services, VA Puget Sound Health Care System, Seattle, WA |
| Dec. 1998 – March 1999 | Member, Search Committee for Assistant Professor of Medicine, University of Washington |

| | |
|---|---|
| 1999 - 2008 | Member, Departmental Budget Council Steering Committee, Department of Orthopaedics & Sports Medicine, University of Washington |
| 1999 - Present | Member, Residency Review Committee, Department of Orthopaedics & Sports Medicine, University of Washington |
| Nov. 17 - 19, 1999 | Participant, Northwest Network Clinical Retreat, Coeur d'Alene, ID, sponsored by The Department of Veterans Affairs, VA Learning University |
| June 2000 – June 2001 | Member, Search Committee for Chief of Surgery/Vice-Chairman Dept. of Surgery, VAMC/University of Washington School of Medicine |
| 2003 | Member, Search Committee for Orthopaedic Spine Surgeon, Department of Orthopaedics & Sports Medicine, University of Washington School of Medicine |
| 2004 | Member, Search Committee for Orthopaedic Oncologist, Department of Orthopaedics & Sports Medicine, University of Washington School of Medicine |
| 2004 | Member, Search Committee for General Oncologic Surgeon, VA Puget Sound Health Care System, Seattle Division |
| 2004 | Member, Search Committee for General Surgeon, VA Puget Sound Health Care System, Seattle Division |
| 2004 – 2006 | Member, VA/UW Executive Development Program, VA Puget Sound Health Care System, VISN 20 |
| 2004 – 2006 | Senator, Faculty Senate, University of Washington |
| 2004 – Present | Board Member, Board of Directors, Cancer Research and Biostatics (CRAB), Seattle, Washington |
| 2007 | Chair, Search Committee for Chief of Radiology & Diagnostic Services, VA Puget Sound Health Care System |
| 2008 | Field Advisory Committee for Orthopaedics, Veterans Administration Healthcare System |
| 2009 - 2011 | Member, Search Committee for Chair, Department of Orthopaedics and Sports Medicine, University of Washington School of Medicine |
| 2010 | Chair, Search Committee for UWMC Oncology Faculty member, Department of Orthopaedics and Sports Medicine, University of Washington School of Medicine |

| | |
|---|---|
| 2010 – 2011 | Chair, Search Committee for Harborview Trauma Faculty member, Department of Orthopaedics and Sports Medicine, University of Washington School of Medicine |
| 2010 – Present | Member, VISN 20 Surgical Strategic Planning Workgroup, Veterans Health Administration |
| June 29 – 30, 2010 | Inaugural UW Medicine Patients First Leadership Development Institute Conference, Seattle |
| November 2 – 3, 2010 | UW Medicine Patients First Leadership Development Institute Conference, Seattle |
| February 2, 2011 | UW Medicine Patients First Leadership Development Institute Conference, Seattle |
| May 10, 2011 | UW Medicine Patients First Leadership Development Institute Conference, Seattle |
| September 27, 2011 | UW Medicine Patients First Leadership Development Institute Conference, Seattle |
| October, 2011 – present | Member, Search Committee for Chief of Anesthesiology, VA Puget Sound Health Care System |

## RESEARCH FUNDING

A. PREVIOUSLY FUNDED PROJECTS

Zimmer Incorporated: Molecular studies of chondrosarcoma cell lines and EXT genes, Principal Investigator, $120,000. 1998-2001.

Biopure Incorporated: A multicenter, randomized, single-blind red blood cell-controlled, parallel group study to evaluate the effect on allogeneic red blood cell use and the safety of room temperature stable hemoglobin-based oxygen carrier-201 (HBOC-201) when administered therapeutically and perioperatively in orthopaedic surgery patients who have not received erythropoietin nor undergone autologous blood donation. Site Co-Investigator at VAPSHCS, $78,000. 1999-2000.

Orthopaedic Research and Education Foundation: The Role of Sarcoma Fusion Proteins in the Genesis of Ewing's Sarcoma, Principal Investigator, $100,000. 2002-2004.

Florence and Marshall Schwid Memorial Foundation: The Role of Wild-type TLS and the TLS/CHOP Sarcoma Fusion Protein in the Genesis of Myxoid Liposarcoma, Principal Investigator, $50,000. 2003-2004.

B. ACTIVELY FUNDED PROJECTS

Veterans Administration Merit Review: Functional Analysis of EWS/FLI-1, Principal Investigator, $527,700. 2005 – 2009.

Veterans Administration Merit Review: The EWS/FLI-1 Fusion Protein and RNA Splicing in Ewing's Sarcoma, Principal Investigator, $270,000. 2002-2005.

National Institutes of Health: TLS and TLS Leukemia Fusion Protein, Co-Investigator, $680,000. 2002-2006.

Musculoskeletal Transplant Foundation / OREF Herndon Research Residency Awards: Splicing Factors Effect Chondrocyte Differentiation and Collagen Synthesis, Principal Investigator (Resident Principal Investigator: Eric Klineberg, M.D.), $15,000. 2004.

National Institutes of Health: Chondrogenesis and histone modification enzymes, Co-investigator, $1,225,000. 2004-2009.

## BIBLIOGRAPHY

A. MANUSCRIPTS IN REFEREED JOURNALS

1) **Chansky HA**, Iannotti JP: The vascularity of the rotator cuff. *Clin Sports Med* 1991 Oct; 10(4):807-822.

2) Lazarus M, **Chansky HA**, Misra S, Williams GR, and Iannotti JP: Comparison of open and arthroscopic subacromial decompression. *J Shoulder Elbow Surg* 1994 3:1011.

3) Simonian PT, Conrad EU, Chapman JR, Harrington RM, and **Chansky HA**: Effect of sterilization and storage treatments on screw pullout strength in human allograft bone. *Clin Orthop* 1994 302:290-296.

4) Raskind WH, Conrad EU, **Chansky HA,** and Matsushita M: Loss of heterozygosity in chondrosarcomas for markers linked to hereditary multiple exostoses loci on chromosomes 8 and 11. *Am J Hum Genet* 1995 56:1132.

5) Conrad EU 3rd, Bradford L, **Chansky HA**: Pediatric soft-tissue sarcomas. *Orthop Clin North Am* 1996 Jul;27(3):655-64. Review.

6) **Chansky HA,** Robbins JR, Cha S, Raskind WH, Conrad EU, and Sandell LJ: Expression of cartilage extracellular matrix and potential regulatory genes in a new chondrosarcoma cell line. *J Orthop Res* 1998 16:521-530.

7) **Chansky HA**, Trumble TE, Conrad EU 3rd, Wolff JF, Murray LW, Raskind WH: Evidence for a polyclonal etiology of palmar fibromatosis. *J Hand Surg* 1999 24A:339-344.

8) Aigner T, Zhu Y, **Chansky HA**, Matsen FA, Maloney WJ, Sandell LJ: Reexpression of procollagen type IIA by adult articular chondrocytes in osteoarthritic cartilage. *Arthritis Rheum* 1999 42:1443-50.

9) Huang FS, Simonian PT, **Chansky HA**: Irreducible posterolateral dislocation of the knee: a case report with video illustration. *Arthroscopy* 2000 16(3)(April):1-6.

10) Yang L, **Chansky HA**, Hickstein DD: EWS/Fli-1 fusion protein interacts with hyperphosphorylated RNA polymeraseII and interferes with serine-arginine protein-mediated RNA splicing. *J Biol Chem* 2000 Dec 1;275(48):37612-8.

11) **Chansky HA**, Hu, M, Hickstein DD, Yang L: Oncogenic TLS/ERG and EWS/Fli-1 fusion proteins inhibit RNA splicing mediated by YB-1 protein. *Cancer Res* 2001 May 1;61(9):3586-90.

12) Yang L, Xia L, Wu DY, Wang H, **Chansky HA**, Schubach WH, Hickstein DD, Zhang Y: Molecular cloning of ESET, a novel histone H3-specific methyltransferase that interacts with ERG transcription factor. *Oncogene* 2002 Jan 3;21(1):148-52.

13) Clinton JM, **Chansky HA**, Odell DD, Zielinska-Kwiatkowska A, Hickstein DD, Yang L: Characterization and expression of the human gene encoding two translocation liposarcoma protein-associated serine-arginine (TASR) proteins. *Gene* 2002 Feb 6;284(1-2):141-7.

14) Billingsley KG, Schwartz DL, Lentz S, Vallieres E, Montgomery RB, Schubach W, Penson D, Yueh B, **Chansky HA**, Zink C, Parayno D, Starkebaum G: The development of a telemedical cancer center within the Veterans Affairs Health Care System: a report of preliminary clinical results. *Telemed J E Health* 2002 Spring;8(1):123-30.

15) Rapp TB, Yang L, Conrad EU 3rd, Mandahl N, **Chansky HA**: RNA splicing mediated by YB-1 is inhibited by TLS/CHOP in human myxoid liposarcoma cells. *J Orthop Res* 2002 Jul;20(4):723-9.

16) Amory JK, **Chansky HA**, Chansky KL, Camuso MR, Hoey CT, Anawalt BD, Matsumoto AM, Bremner WJ: Preoperative supraphysiological testosterone in older men undergoing knee replacement surgery. *J Am Geriatr Soc* 2002 Oct;50(10):1698-1701.

17) Yang L, Mei Q, Zielinska-Kwiatkowska A, Matsui Y, Blackburn ML, Benedetti D, Krumm A, Taborsky Jr GJ, **Chansky HA**: An ERG (ETS-related gene)-associated histone methyltransferase interacts with histone deacetylases and transcription co-repressors mSin3 A/B. *Biochem J* 2003 Feb 1;369(Pt 3):651-7.

18) Matsui Y, **Chansky HA**, Barahmand-Pour F, Zielinska-Kwiatkowska A, Tsumaki N, Myoui A, Yoshikawa H, Yang L, Eyre DR: COL11A2 collagen gene transcription is differentially regulated by EWS/ERG sarcoma fusion protein and wild-type ERG. *J Biol Chem* 2003 Mar 28;278(13):11369-75.

19) Herbst KL, Amory JK, Brunzell JD, **Chansky HA**, Bremner WJ: Testosterone administration to men increases hepatic lipase activity and decreases HDL and LDL size in 3 wk. *Am J Physiol Endocrinol Metab* 2003 Jun;284(6):E1112-8.

20) Blackburn ML, **Chansky HA**, Zielinska-Kwiatkowska A, Matsui Y, Yang L: Genomic structure and expression of the mouse ESET gene encoding an ERG-associated histone methyltransferase with a SET domain. *Biochim Biophys Acta* 2003 Oct 1;1629(1-3):8-14.

21) Clark JM, **Chansky HA**, Mirza SK: Toward better interaction between orthopaedists and researchers. *J Bone Joint Surg Am* 2003 Nov;85-A(11):2249-51.

22) Zou J, Barahmand-Pour F, Blackburn ML, Matsui Y, **Chansky HA**, Yang L: Survival of motor neuron protein SMN interacts with transcription corepressor mSin3A. *J Biol Chem* 2004 Apr 9;279(15):14922-8.

23) **Chansky HA**, Barahmand-Pour F, Kahn-Farooqi W, Zielinska-Kwiatkowska A, Blackburn ML, Chansky K, Conrad EU 3rd, Bruckner JD, Greenlee TK, Yang L: Targeting of EWS/FLI-1 by RNA interference attenuates the tumor phenotype of Ewing's sarcoma cells in vitro. *J Orthop Res* 2004 July;22(4):910-7.

24) Braman JP, Bruckner JD, Clark JM, Norman AG, **Chansky HA**: Articular cartilage adjacent to experimental defects is subject to atypical strains. *Clin Orthop Relat Res* 2005 Jan;(430):202-7.

25) Zou J, Ichikawa H, Blackburn ML, Hu HM, Zielinska-Kwiatkowska A, Mei Q, Roth GJ, **Chansky HA**, Yang L: The oncogenic TLS-ERG fusion protein exerts different effects in hematopoietic cells and fibroblasts. *Mol Cell Biol* 2005 Jul;25(14):6235-6246.

26) Matsushita H, Blackburn ML, Klineberg E, Zielinska-Kwiatkowska A., Bolander ME, Sarkar G, Suva LJ, **Chansky HA,** Yang L. TASR-1 regulates alternative splicing of collagen genes in chondrogenic cells. *Biochem Biophys Res Commun* 2007 356:411-7.

27) Yang L, Clinton JM, Blackburn ML, Zhang Q, Zou J, Zielinska-Kwiatkowska A, Tang BL, **Chansky HA.** Rab23 regulates differentiation of ATDC5 chondroprogenitor cells. *J Biol Chem,* 2008 Apr 18; 283(16):10649-57.

28) Pan J, Zou J, Wu DY, Roberson S, Hennings LJ, Ma XY, Yared M, Blackburn ML, **Chansky HA,** Yang L. TLS-ERG leukemia fusion protein deregulates CDK1 and blocks terminal differentiation of myeloid progeniotor cells. *Mol Cancer Res* 2008 May; 6(5):862-72.

29) Hu HM, Zielinska-Kwiatkowska A, Munro K, Wilcox J, Wu DY, Yang L, **Chansky HA.** EWS/FLI1 suppresses retinoblastoma protein function and senescence in Ewing's sarcoma cells. *J Orthop Res* 2008 Jun; 26(6):886-93.

30) Yang L, Ma X, Lyone A, Zou J, Blackburn ML, Pan J, Yang D, Matsushita H, Mei b, Zielinska-Kwiatkowska A, **Chansky HA**. Proper expression of helix-loop-helix protein Id2 is important to chondrogenic differentiation of ATDC5 cells. *Biochem J* 2009 May 1; 419(3):635-43.

31) Yang L, Hu HM, Zielinska-Kwiatkowska A, **Chansky HA**. FOXO1 is a direct target of EWS-Fli1 oncogenic fusion protein in Ewings's sarcoma cells. *Biochem Biophys Res Commun* 2010 Nov 5, 402(1):129-34.

32) Yang L, Ma XY, Blackburn ML, Matsushita HM, **Chansky HA**. Inhibitor of DNA binding protein 2 regulates chondrocyte differentiation. In revision, *Matrix Biology*.

B. <u>BOOK CHAPTERS</u>

1) Urban M and **Chansky HA**: Innovation evolving: a photographic gallery from the past: *In* Shaffer JL and Steinberg DR (eds.): *The Centennial Edition of the Orthopaedic Journal of the University of Pennsylvania*, 1989.

2) **Chansky HA** and Iannotti JP: The vascularity of the rotator cuff. *In* Hawkins R (ed.): Basic Science and Clinical Application to the Athlete's Shoulder. *Clinics in Sports Medicine*. Philadelphia: Saunders, 1991, 10:807-822.

3) Sandell LJ, **Chansky HA**, Zamparo O, and Herring T: Molecular biology of collagens in normal and osteoarthritic cartilage. *In* Kuettner KE and Goldberg V (eds.): *New Horizons in Osteoarthritis*. Rosemont, IL: AAOS Press, 1995, 117-130.

4) Conrad EU, Bradford L, and **Chansky HA**: Pediatric soft-tissue sarcomas. *In* Stephen D, Heinrich SD and Scarborough MT (eds.): *Orthopaedic Clinics of North America*. Philadelphia: WB Saunders, 1996, 27(3):655-664.

5) **Chansky HA,** O'Donnell R, Howlett AT, and Conrad EU: Common bone tumors. *In* O'Neill JA, Rowe MI, Grosfeld JL, Fonkalsrud EW, and Coran AG (eds.): *Pediatric Surgery*. 5th ed. St Louis: Mosby-Year Book, Inc., 1998.

6) **Chansky HA** and Casciato DA: Bone and joint complications. *In* Casciato DA and Lowitz B (eds.): *Manual of Clinical Oncology*. 5th ed. Boston: Little, Brown and Company, 2000.

7) **Chansky HA:** Metastatic carcinoma. *In* Gellman H (ed): *Orthopaedic Surgery*. eMedicine.com, 2002.

8) Rizvi SS and **Chansky HA**: Myeloma. *In* Gellman H (ed): *Orthopaedic Surgery*. eMedicine.com, 2002.

9) **Chansky HA:** Arthroplasty-associated infections. *In* Gellman H (ed): *Orthopaedic Surgery*. eMedicine.com, 2002.

10) **Chansky HA**: Surgical management of malignant soft-tissue tumors. *In* Menendez L (ed): *Musculoskeletal Tumors: Orthopaedic Knowledge Update*. American Academy of Orthopaedic Surgeons, 2002.

11) **Chansky HA** (Section editor): Orthopaedic surgery, neoplasms. *In* Gellman H (ed): *Orthopedic Surgery*. eMedicine.com, 2003.

12) **Chansky HA** and Casciato DA: Bone and joint complications. *In* Casciato DA (ed): *Manual of Clinical Oncology, 5th ed.* Pennsylvania: Lippincott Williams & Wilkins, 2004.

13) **Chansky HA**: Hip disarticulation and transpelvic amputation: surgical management. *Atlas of Limb Prosthetics, 3rd edition*. American Academy of Orthopaedic Surgeons, 2004.

14) **Chansky HA**, Casciato DA and Berenson JR: Bone and joint complications. *In* Casciato DA (ed): *Manual of Clinical Oncology, 6th ed.* Pennsylvania: Lippincott Williams & Wilkins, 2009.

15) Casciato DA, Berenson JR and **Chansky HA**,: Bone and joint complications. *In* Casciato DA (ed): *Manual of Clinical Oncology,* 7*th ed.* Pennsylvania: Lippincott Williams & Wilkins, in press.

C. OTHER PUBLICATIONS

1) **Chansky HA** and Conrad EU: Tumor-related proteins can help predict the behavior of chondrosarcomas. *University of Washington Dept. of Orthopaedics Research Report*, 1997, 31-32.

2) Zhu Y, **Chansky HA**, Matsen FA III, and Sandell LJ: Differential localization of collagen types I, IIA and III in human osteoarthritic cartilage *University of Washington Dept. of Orthopaedics Research Report*, 1998, 7-8.

3) Norman AG, Doughtery WM, **Chansky HA**, Simonian P, Clark JM, and Sidles J: A new technique for mapping articular cartilage contour and thickness. *University of Washington Dept. of Orthopaedics Research Report*, 1999, 32-33.

4) **Chansky HA**, Robbin JR, Raskind WH, Cha S, Conrad EU, Clark JM, Bruckner JD, and Sandell LJ: Expression of cartilage extracellular matrix and potential regulatory genes in a new human chondrosarcoma cell line. *University of Washington Dept. of Orthopaedics Research Report*, 1999, 38-39.

5) **Chansky HA**, Howlett A, Bosserhoff A, Buettner R, Conrad EU, Sandell LJ: Expression of cartilage-derived retinoic acid sensitive protein (CD-RAP) by chondroid tumors. *University of Washington Dept. of Orthopaedics Research Report*, 2000, 5-6.

6) Rapp T, Yang L, Conrad EU, **Chansky HA:** TLS/CHOP inhibits RNA splicing mediated by YB-1. *University of Washington Dept. of Orthopaedics and Sports Medicine Research Report,* 2001, 8-9.

7) Clinton JM, **Chansky HA,** Zielinska-Kwiatkowska A, Conrad EU, Yang L: Genomic sequences and expression of the RNA splicing factors TASR-1 and TASR-2. *University of Washington Dept. of Orthopaedics and Sports Medicine Research Report,* 2002, 27-29.

8) Odell DD, **Chansky HA,** Zielinska-Kwiatkowska A, Yang L: The role of fusion protein-induced alternative splicing in the development of Ewing's sarcoma. *University of Washington Dept. of Orthopaedics and Sports Medicine Research Report,* 2002, 30-31.

9) **Chansky HA**, Zielinska-Kwiatkowski A, Matsui Y, Blackburn M, Conrad EU, Bruckner JD, Yang L: RNA interference suppresses expression of EWS/FLI-1 in Ewing's sarcoma cells. *University of Washington Dept of Orthopaedics and Sports Medicine Research Report,* 2003, 23-25.

10) Matsui Y, **Chansky HA**, Barahmand-pour F, Zielinska-Kwiatkowska A, Tsumaki N, Kyoui A, Yoshikawa H, Yang L, Eyre DR: COL11A2 collagen gene transcription is differentially regulated by EWS/ERG sarcoma fusion protein and wild-type ERG. *University of Washington Dept. of Orthopaedics and Sports Medicine Research Report,* 2003, 58-59.

11) Klineberg EO, **Chansky HA**, Blackburn M, Zielinska-Kwiatkowska A, Yang L: Serine-arginine proteins regulate alternative splicing of type II collagen. *University of Washington Dept. of Orthopaedic and Sports Medicines Research Report*, 2004, 28-31.

12) **Chansky HA**, Barahmand-Pour F, Kahn-Farooqi W, Zielinska-Kwiatkowska A, Chansky K, Conrad EU, Bruckner JD, Greenlee TK, Yang L: Targeting of EWS/FLI-1 by RNA interference attenuates the tumor phenotype of Ewing's sarcoma cells. *University of Washington Dept. of Orthopaedics and Sports Medicine Research Report*, 2004, 32-34.

13) Hu HM, Munro K, Yang L, **Chansky HA**: EWS/FLI-1 inhibits cellular senescence and promotes proliferation in Ewing's sarcoma cells. *University of Washington Dept. of Orthopaedics and Sports Medicine Research Report*, 2005, 44-45.

14) Hu HM, Zielinska-Kwiatkowska A, **Chansky HA**: EWS/FLI-1 tumor protein inhibits senescence of Ewing's sarcoma cells. *University of Washington Dept. of Orthopaedics and Sports Medicine Research Report*, 2006, 30-31.

15) Hu HM, Zielinska-Kwiatkowska A, Wu D, Yang L, **Chansky H:** A gene-therapy approach to suppressing EWS/FLI-1 leads to cellular senescence through Rb family dependent and independent pathways. *University of Washington Dept. of Orthopaedics and Sports Medicine Research Report,* 2007, 10-11.

16) Yang L, Ma X, Zielinska-Kwiatkowska A, **Chansky HA**: Inhibitor of DNA binding protein Id2 negatively regulates chondrogenic differentiation of ATDC5 cells. *University of Washington Dept. of Orthopaedics and Sports Medicine Research Report,* 2007, 12-13.

## D. ABSTRACTS & PRESENTATIONS

1) Craythorne C, Pollack SR, Brighton CT, and **Chansky HA:** The progressive alteration of the zeta potential of rat bone in relation to two models of osteoporosis. BRAGS, 10th Annual Meeting, Philadelphia, PA, 1991.

2) Lazarus M, **Chansky HA**, Iannotti JP, Williams J: Open versus arthroscopic subacromial decompression for the treatment of impingement syndrome. Pennsylvania Orthopaedic Society, Pittsburgh, PA. November, 1992. Awarded First Prize for a Resident Paper.

3) Lazarus M, Iannotti JP, Williams J, and **Chansky HA**: Comparison of open and arthroscopic subacromial decompression for impingement syndrome. Scientific Program of the Annual Meeting of the American Academy of Orthopaedic Surgeons, 1993.

4) Raskind WH, Conrad EU, **Chansky HA**, Robbins, JR, and Sandell LJ: Loss of heterozygosity for markers on chromosome 8q in a human chondrosarcoma cell line and in a tumor that developed in a man with hereditary multiple exostoses (HME). American Society of Human Genetics, 1994.

5) Sandell LJ, Raskind WH, **Chansky HA**, Robbins JR, and Conrad EU: Characterization of a human chondrosarcoma cell line synthesizing abundant aggrecan and no fibrillar collagens or decorin. *Trans Ortho Res Soc*, 19:750, 1994.

6) Hoekema J, **Chansky HA,** Bruckner J, Cusick K, Nelson K, and Conrad EU: Clinical and immunologic evaluation of allograft transplantation for malignant and aggressive bone tumors. Slide presentation at the joint meeting of the European Musculo-Skeletal Oncology Society and the American Musculo-Skeletal Tumor Society and 8th Annual International Symposium on Limb Salvage (ISOLS), Florence, Italy, May 1995. Abstract published in proceedings thereof.

7) Conrad EU, **Chansky HA,** Gretch DR, Obermeyer KR, Moogk MS, Sayers M, Wilson JJ, et al: The transmission of hepatitis C virus by tissue transplantation. Poster presentation at the joint meeting of the European Musculo-Skeletal Oncology Society and the American Musculo-Skeletal Tumor Society and 8th Annual International Symposium on Limb Salvage (ISOLS), Florence, Italy, May 1995. Abstract published in proceedings thereof.

8) **Chansky HA**, Robbins J, Conrad EU, Raskind W, and Sandell LJ: A human chondrosarcoma cell line with a mutation of the p53 tumor suppressor gene. *Trans Ortho Res Soc*, 20:1995.

9) **Chansky HA,** Cunningham R, Gown A, Giachelli CM, and Conrad EU: Osteopontin: a molecular marker of both notochord and chordoma. Connective Tissue Oncology Society, Boston, MA, September 1995.

10) **Chansky HA,** Cunningham R, Gown A, and Conrad EU: Tumor-related genes and chordoma: an immunohistochemical study. Connective Tissue Oncology Society, Boston, MA, September 1995.

11) **Chansky HA,** Cunningham R, Gown A, Sandell LJ, and Conrad EU: Immunostaining of tumor-related proteins and grading of cartilage neoplasms. Connective Tissue Oncology Society, Boston, MA, September 1995.

12) **Chansky HA,** Cunningham R, Gown A, Giachelli CM, and Conrad EU: Osteopontin: a molecular marker of both notochord and chordoma. Orthopaedic Research Society, Atlanta, GA, February 1996.

13) **Chansky HA,** Cunningham R, Howlett A, Gown A, and Conrad EU: The prognostic value of tumor-related proteins in chondrosarcoma. Musculoskeletal Tumor Society, Seattle, WA, May 1996.

14) Ichimura S, Wu JJ, **Chansky HA,** Sandell LJ, and Eyre DR: Novel chain assembly of type XI collagen in a human chondrosarcoma cell line. Orthopaedic Research Society, San Francisco, CA, February 1997.

15) Howlett AT, **Chansky HA**, Eary JF, and Conrad EU: Quantitative (F-18) fluorodeoxyglucose positron emission tomography (FDG PET) assessment of tumor grade and response to neoadjuvant chemotherapy. Poster presentation/scientific exhibit, American Academy of Orthopaedic Surgeons Annual Meeting, San Francisco, CA, February 1997.

16) **Chansky HA,** Cunningham R, Howlett AT, Gown A, Bruckner JD, and Conrad EU: The prognostic value of tumor-related proteins in chondrosarcoma. American Academy of Orthopaedic Surgeons, San Francisco, CA,. February 1997.

17) **Chansky HA,** Howlett AT, Bosserhoff AK, Oganesian A, Conrad EU, and Sandell LJ: Expression of a cartilage-derived retinoic acid sensitive protein (CD-RAP) by chondroid tumors. Orthopaedic Research Society San Francisco, CA, February 1997.

18) **Chansky HA,** Kieras J, Schwid H, Amory J, Long D, Wyllie B: An integrated same-day services program in an urban VA medical center improves patient care. Seattle Surgical Society Annual Scientific Program, Seattle, WA, January 10, 1998.

19) Howlett AT, **Chansky HA**, O'Donnell RJ, Conrad EU, et al: Soft tissue sarcoma in adults with AIDS and relation to Epstein-Barr virus infection. American Federation for Medical Research meeting, Carmel, CA, February 1998.

20) Howlett AT, **Chansky HA**, Conrad EU, et al: Treatment of aneurysmal bone cysts with curettage, cryotherapy, and bone grafting. Accepted for poster presentation at the

American Academy of Orthopaedic Surgeon's Annual Meeting, New Orleans, LA, March 1998.

21) Howlett AT, **Chansky HA**, Conrad EU, et al: Sarcoma heterogeneity in FDG PET scan uptake: correlation with histopathologic findings. American Pathology Society annual meeting, New York City, NY, April 1998.

22) O'Donnell RJ, Bruckner JD, O'Neal PD, **Chansky HA**, Conrad EU: Condyle sparing and intercalary resections about the knee. The 4th International Combined Meeting of the American and European Musculoskeletal Tumor Societies, Washington, DC, May 7-10, 1998.

23) Randall RL, Lloyd C, **Chansky HA**, Bruckner JD, Conrad EU: Sacral resection in the management of malignant disease and tumor-like conditions. The 4th International Combined Meeting of the American and European Musculoskeletal Tumor Societies, Washington, DC, May 7-10, 1998.

24) Conrad EU, Bruckner JD, **Chansky HA**, O'Neal PD, Nelson K: Allograft antibodies: do they predict allograft complications? The 4th International Combined Meeting of the American and European Musculoskeletal Tumor Societies, Washington, DC, May 7-10, 1998.

25) Randall RL, Gollogly S, Papenhausen MD, Bruckner J, **Chansky HA**, Conrad EU: Errors of diagnosis and margin determination of soft tissue sarcomas initially treated at non-tertiary medical centers. The 4th International Combined Meeting of the American and European Musculoskeletal Tumor Societies, Washington, DC, May 7-10, 1998.

26) Norman AG, Dougherty WM, **Chansky HA**, Simonian PT, Sidles JA, Clark JM: A new technique for mapping articular cartilage contour and thickness. The 45th Annual Meeting, Orthopaedic Research Society, Anaheim, CA, February 1-4, 1999.

27) Switzer JA, Norman AG, **Chansky HA**, Clark JM: Importance of surface integrity to healing of articular cartilage defects. The 45th Annual Meeting, Orthopaedic Research Society, Anaheim, CA, February 1-4, 1999.

28) Amory J, **Chansky HA**, Chansky K, Hoey C, Anawalt BD, Matsumoto AM and Bremner WJ: The effects of supraphysiologic testosterone on functional outcomes after joint replacement surgery in elderly men. Endocrine Society, 1999, #OR9-3.

29) Clinton J, **Chansky HA**, Yang L: Cloning and sequencing of the TLS-associated splicing factors TASR-1 and TASR-2. Medical Student Research Meeting, Carmel, CA, February 2001.

30) **Chansky HA**, Yang L: The transcription and translation factor YB-1 interacts with oncoprotein TLS and regulates RNA splicing. Orthopaedic Research Society, San Francisco, CA, February 2001.

31) Yang L, **Chansky HA**: Ewing's sarcoma fusion protein EWS/FLI-1 interferes with EWS-mediated RNA splicing . Orthopaedic Research Society, San Francisco, CA, February 2001.

32) Clinton J, **Chansky HA**, Odell D, Zielinska-Kwiatkowska A, Yang L: Characterization and expression of the human TASR-1 gene. Orthopaedic Research Society, Dallas, TX, February 2002.

33) Yang L, Jaishankar S, Baker S, **Chansky HA**: Cellular transformation by EWS/FLI-1 is associated with disruption of RNA splicing. Orthopaedic Research Society, Dallas, TX, February 2002.

34) Camuso M, **Chansky HA**, Amory J, Chansky K, Bremner W: Supraphysiologic testosterone administration in elderly men undergoing total joint arthroplasty. American Academy of Orthopaedic Surgeons, Dallas, TX, February 2002.

35) **Chansky HA**, Zielinska-Kwiatkowska A, Matsui Y, Blackburn M, Yang L: RNA interference suppresses expression of EWS/FLI-1 in Ewing's sarcoma cells Orthopaedic Research Society, New Orleans, LA, February 2003.

36) Blackburn M, **Chansky HA**, Matsui Y, Zielinska-Kwiatkowska A, Yang L: Gene structure and expression of an ERG-associated H3-specific histone methyltransferase with SET Domain (ESET). Orthopaedic Research Society, New Orleans, LA, February 2003.

37) Matsui Y, **Chansky HA**, Zielinska-Kwiatkowska A, Tsumaki N, Myoui A, Yoshikawa H, Yang L, Eyre DR: Ewing's sarcoma pathobiology: ERG and EWS/ERG differentially regulate COL11A2 gene expression. Orthopaedic Research Society, New Orleans, LA, February 2003.

38) Matsui Y, **Chansky HA**, Yang L, Eyre DR, Tsumaki N, Yoshikawa H, Suzue N, Yasui N: SAOS-2 osteosarcoma cells use EWS/ERG-responsive CIS-elements to induce Col11A2 collagen gene expression. Orthopaedic Research Society, San Francisco, CA, March 2004.

39) Yang L, Barahmand-pour F, Zielinska-Kwiatkowska A, Blackburn ML, Klineberg E, Hatano H, Sarkar G, Bolander ME, **Chansky HA**: Serine-arginine proteins regulate alternative splicing of type II collagen. Orthopaedic Research Society, San Francisco, CA, March 2004.

40) **Chansky HA**, Blackburn M, Khan-Farooqi W, Benedetti D, Yang L: Expression array analysis of a Ewing's sarcoma cell line following knockdown of EWS/Fli-1 by RNA interference. Orthopaedic Research Society, San Francisco, CA, March 2004.

41) **Chansky HA**, Yang L, Hu HM: RNA Interference Workshop: Target validation and potential therapeutic applications for childhood cancer. Sponsored by the Cancer Therapy Evaluation Program, National Cancer Institute and NIH Office of Rare Diseases, and Children's Oncology Group, Arlington, Virginia, September 28-30, 2004.

42) Goto T, Matsui Y, Yukata K, Kubo T, **Chansky HA**, Yang L, Eyre DR, Yasui N: SP1 family of transcription factors and histone deacetylases regulate alpha 2 type XI collagen gene expression in osteosarcoma-derived SAOS-2 cells. Orthopaedic Research Society, Washington D.C., February 2005.

43) Yang, L, Clinton, J, Zielinska-Kwiatkowska, A, Blackburn, M, Matsushita, H, Mei, B, **Chansky, HA**: Screening for genes involved in chondrocyte differentiation through

random mutagenesis introduced by retroviral insertion. Orthopaedic Research Society, Chicago, IL, March 2006.

44) Hu H, Munro K, Zielinska-Kwiatkowska A, Yang L, **Chansky HA**: FKHR is upregulated and cyclin D1 is downregulated after RNAi-mediated knockdown of EWS/FLI-1 in Ewing's sarcoma cell lines. Orthopaedic Research Society, Chicago, IL, March 2006.

45) Hu HM, Munro K, Wu D, Yang L, **ChanskyHA:** EWS/FLI-1 inhibits cellular senescence in Ewing's sarcoma cell lines. Orthopaedic Research Society, Chicago, IL, March 2006.

46) Hu H, Zielinska-Kwiatkowska A, Wu DY, Yang L, **Chansky HA**: EWS/FLI-1 inhibits cellular senescence through Rb family-dependent and -independent pathways. Orthopaedic Research Society, San Diego, CA., February 2007.

47) Yang L, Ma XY, Blackburn ML, Matsushita H, **Chansky HA**: Inhibitor of DNA binding protein 2 (Id2) regulates chondrocyte differentiation. Orthopaedic Research Society, San Diego, CA, March 5-8, 2007.

48) Zou J, Matsushita H, Blackburn ML, Zielinska-Kwiatkowska A, **Chansky HA**, Yang L. ESET histone methyltransferase inhibits chondrogenic differentiation through down-regulation of Sox9. Orthopaedic Research Society, San Francisco, CA, March 2-5, 2008.

49) Humbyrd C, Hu HM, Zielinska-Kwiatkowska A, Yang L, **Chansky HA.** The EWS/FLI-1 fusion protein modulates expression of hypoxia-inducible factor 1α (hif-1α). Orthopaedic Research Society, San Francisco, CA, March 2008.

50) Yang L, Clinton JM, Blackburn ML, Zhang Q, Zielinska-Kwiatkowska A, **Chansky HA.** Rab23 regulates differentiation of ATDC5 chondroprogenitor cells. Orthopaedic Research Society, San Francisco, CA, March 2-5, 2008.

51) Yang L, Zielinska Kwiatkowska A, Zou J, **Chansky H.** Id2 inhibitor of DNA-binding protein is important to chondrogenic differentiation. Orthopaedic Research Society, Las Vegas, NV, February 22-25, 2009.

52) Yang L, Zielinska-Kwiatkowska A, Zou J, **Chansky H.** Inhibition of Ewing's sarcoma cells by a novel small molecule compound. Orthopaedic Research Society, Las Vegas, NV, February 22-25, 2009.

53) Yang L, Zou J, Zielinska Kwiatkowska A, Matsushita H, Blackburn ML, Pan J, **Chansky HA**. ESET histone methyltransferase is required for Sox9 function and essential for chondrogenic differentiation. Orthopaedic Research Society, New Orleans, LA, March 6-9, 2010.

54) Yang L, Zielinska Kwiatkowska A, Hu H-M, **Chansky HA**. Functional analysis of inducible EWS-Fli1 knockdown in Ewing's sarcoma cells. Orthopaedic Research Society, New Orleans, LA, March 6-9, 2010.

55) Yang L, Zielinska-Kwiatkowska A; Chansky HA. In vivo effects of Type II EWS-Fli1 expression in mesenchymal cells. Orthopaedic Research Society, Long Beach, CA, January 13, 2011.

# Hyaluronic Acid/ Viscosupplementation (Re-review)

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November 2013




## Abbreviations

- HA, hyaluronic acid
- MA, meta-analysis
- IACS, intraarticular corticosteroids
- ITT, intention-to-treat
- NSAIDS, nonsteroidal anti-inflammatory drugs
- OA, osteoarthritis
- OR, odds ratio
- Pt, patient
- RR, relative risk
- RCT, randomized controlled (or comparator) trial
- SMD, standardized mean difference (also referred to as effect size)
- SR, systematic review
- WMD, weighted mean difference
- WOMAC, Western Ontario McMasters University Index

## Shorthand references

- **2009 Bannuru review**, *HA vs IACS* (Bannuru et al., 2009)
- **2010 report**, report presented to WA HCA, May 2010
- **2011 Bannuru review**, MA of *trajectory of effect* (versus placebo) over time (Bannuru et al., 2011)
- **Bellamy review**, 2006 Cochrane Review (Bellamy et al., 2006)
  - Included in 2007 Samson review
- **Colen review**, 2012 MA (Colen et al., 2012)
- **Reichenbach review**, MA of *hylan vs HA* (Reichenbach et al., 2007)
- **Rutjes review**, 2012 MA (Rutjes et al., 2012)
- **Samson review**, 2007 HTA prepared for AHRQ (Samson et al., 2007)
- **Update report**, current report for WA HCA


3

## Background

- Knee OA, most common form of OA
  - 6% > 30 yrs
  - 9.5%–12.1% > 60 yrs
- Treatment
  - Nonpharmacological therapy, e.g., physical therapy
  - Acetaminophen
  - NSAIDs (downside: gastrointestinal, cardiovascular events)
  - IACS (downside: short-lived benefits, damage with long-term use)


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## HA/Viscosupplementation

- Replaces depleted natural HA
  - Viscous lubricant, elastic shock absorber
- FDA approved
  - Euflexxa (Bio-HA) (Ferring)
  - Gel-One (Zimmer Inc./Seikagaku Corporation)
  - Hyalgan (Sanofi-Aventis/Fidia)
  - Orthovisc (DePuy Mitek Inc./Anika Therapeutics)
  - Supartz (Artz, Artzal) (Bioventus/Seikagaku)
  - Synvisc and Synvisc-One (Genzyme)
- Cross-linked hyaluronan chains: Highest molecular weight
  - Synvisc (*Hylan G-F 20, hylan*)
  - Gel-One (approved since 2010 report)
- Non-cross-linked HA




## Policy context

- 2010 conclusion:
  - Lower mean pain scores and improved mean function a few weeks after treatment, peaking at 3 mos.
  - Magnitude of benefit of HA alone may be too small to be clinically important.
- 3 new SRs with MA (2011-2012)
  - Safety concerns raised by 1 SR
- Updated guidelines, more negative
  - American Association of Orthopaedic Surgeons (AAOS)
  - American College of Rheumatology (ACR)
- No CMS National Coverage Determination

## PICO

**Populations**: Adults with OA of the knee
**Intervention**: Viscosupplementation (HA injection – Hyalgan, Synvisc, Supartz, Orthovisc, Euflexxa, Gel-One)
**Comparators**: NSAIDs, corticosteroid injection, physical therapy, oral pain medications, placebo, arthroscopic lavage and/or debridement
**Outcomes**: Pain, function, quality of life, adverse events


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## Key questions

1. (a) What is the **clinical effectiveness** of viscosupplementation for treatment of OA of the knee? (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?


8

# Methods

- Search time frame
  - From December 2009 forward
  - Last search July 5, 2013
- Eligible studies
  - SRs
  - RCTs (controlled or comparator)
  - For KQ #2 (safety) and KQ #3 (differential effectiveness): Observational studies
  - For KQ #4 (cost): Any cost study or economic evaluation
- Quality assessment
  - Hayes methodology (similar to GRADE)




# Evidence selection (red=new evidence)

| KQ | SRs with MA (6 Total) | RCTs (4 New) | Other |
|---|---|---|---|
| #1a | **5 SRs:** Samson 2007 (Bellamy 2006), *Bannuru 2009 (HA vs IACS)*) *Bannuru 2011 (efficacy over time),* Colen 2012, Rutjes 2012 | **3 RCTs** Altman 2011; Navarro-Sarabia 2011; Strand 2012a, Strand 2012b | --- |
| #1b | **2 SRs, comparator RCTs:** Reichenbach 2007, Colen 2012 **1 SR, indirect comparison:** Rutjes 2012 | **1 RCT** Petrella 2011 | --- |
| #2 | **2 SRs**: Samson 2007 (Bellamy 2006), Rutjes 2012 | **22 RCTs** w/ sample sizes ≥200; overlap w/ SRs | **4 case series:** 3 in Samson review; Foti 2011.**1 narrative review:** Goldberg and Coutts |
| #3 | **2 SRs:** Samson 2007 (Wang 2004), Rutjes 2012 | **8 RCTs:** All published 2009 or earlier | **1 before-and-after:** Anandacoomarasamy 2008 |
| #4 | **4 economic evaluations:** Torrance et al., 2002; Kahan et al., 2003; Yen at al., 2004; NICE, 2008 | | |

# An explanation, Samson review

- 2007 AHRQ technology assessment
- Covered 6 MAs
- Largest and most comprehensive: Bellamy 2006
  - Cochrane Review
  - Pooled estimates highlighted in update report
- Others:
  - Lo 2003
  - Wang 2004
  - Arrich 2005
  - Modowal 2005
  - Strand 2006


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# Findings, Key Question #1a: preview

| Outcome *# Studies)* | Direction of Findings *(Quality of Evidence)* |
|---|---|
| **Pain** * *4 good SRs w/ MA + 1 RCT=81 RCTs total, >10,000 pts* |  *(moderate)* |
| **Physical function*** *3 good SRs w/ MA)* |  *(moderate)* |
| **Quality of life*** *6 fair-good RCTs, 2147 pts* |  *(moderate)* |
| **Repeat course*** *3 RCTs w/ high dropout)* |  *(low)* |

**Generally placebo-controlled trials (saline injection)*


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Clinical relevance of pain and function improvement – *stay tuned*.


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## Findings, Key Question #1a: preview (cont.)

| Outcome<br>*# Studies* | Direction of Findings<br>*(Quality of Evidence)* |
|---|---|
| **Responder rates**<br>*11 placebo-controlled RCTs w/ deficiencies* | ↑ *(low)* |
| **Responder rates**<br>*2 good pragmatic RCTs* | ↑ *(moderate , generalizability?)* |
| **Versus NSAIDs**<br>*4 RCTs reviewed by Bellamy 2006* | = *(study quality not available)* |
| **Versus IACS**<br>*1 fair-good SR, study quality poor* | HA longer lasting *(low)* |
| **Versus glucosamine and/or chondroitin** | ? *(no evidence)* |


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# Typical trial participants

- Age 53–71 yrs
- Sex distribution varied widely
- Body mass index 29–33 kg/m$^2$
- OA duration 6–9 yrs
- Severity Kellgren–Lawrence grade 2–3 (0–4 scale)
- Baseline pain 42–60 on 100–mm scales or equivalent
- NSAIDs previously tried
- No IACS within previous 3 mos
- Concomitant pain medication allowed (~67% of larger studies disallowed NSAIDs; washout period)
- Not reported: History of trauma; compliance prior to trial; use of IACS previously or during study


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# Findings, Key Question #1a: pain at ~3 mos*

**Peak effect according to 3 SRs with MA.*

- Weight-bearing pain, VAS (**Bellamy 2006**)
  - **WMD –11.0** (CI, –17.8 to –8.2); $I^2$=82% (21 RCTs, 2090 pts)
- VAS preferred (**Colen 2012**)
  - **WMD –10.20** (CI, –15.97 to –4.42); $I^2$=92% (18 RCTs, 2801 pts)
- Weight-bearing pain, WOMAC (**Bellamy 2006**)
  - **SMD –1.0** (CI, –1.6 to –0.5); $I^2$=88% (7 RCTs, 639 pts)
- WOMAC preferred (**Rutjes 2012**)
  - All trials: **SMD –0.37** (CI, –0.46 to –0.28); *P*<0.001; $\tau^2$=0.09, *P*<0.001 for heterogeneity (68 RCTs, 9617 pts)
  - n≥100/grp+adequate assessor blinding: SMD –0.11 (CI, –0.18 to –0.04); $\tau^2$=0.01 (18 RCTs, 5094 pts)
- *Moderate quality:* Large # fair–good RCTs, good MAs, consistent direction/significance of pooled estimates but inconsistency across studies


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# Findings, Key Question #1a: physical function at ~3 mos*

**No clear pattern for peak function effects (Bannuru 2011)*

- Weight-bearing pain, WOMAC (**Bellamy 2006**)
  - **SMD -0.9** (CI, -1.3 to -0.4); $I^2$=84%
- WOMAC preferred (**Rutjes 2012**)
  - All trials: **SMD -0.33** (CI, -0.43 to -0.22); *P*<0.001; $\tau^2$=0.10, *P*<0.001 for heterogeneity
  - n=100/grp+adequate assessor blinding: SMD -0.09 (CI, -0.17 to -0.00); $\tau^2$=0.01 (15 RCTs, 4296 pts)

*Moderate quality:* Same considerations as for pain


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# Clinical relevance: mean *within-group or individual* improvement from baseline

| Source | Term Used | Definition |
|---|---|---|
| **Samson review** | Positive response, pain | **20- to 40-point** improvement, WOMAC pain (100-point scale) |
| **Colen review** | MCID, pain | **10- to 30-point** improvement, 100-point scale |
| **4 RCTs** | Clinical response, pain | **≥20-point** improvement, 100-point scale |
| **OMERACT-OARSI** (used by 5 RCTs) | Clinical response, pain or function | **≥20% or ≥10 mm** (100-mm VAS ) , **2 subscales**: (a) WOMAC pain, (b) WOMAC physical function, or (c) patient global assessment |
| | Strict clinical response | Pain or physical function: **≥50% and ≥20 mm** on 100-mm VAS |
| **IMMPACT (Dworkin 2008)** | MCID, pain | **10% to 20% or 1 cm** (10-cm VAS)/**10 mm** (100-mm VAS) |
| | Moderate (clinically important) improvement | **30% or** 2.0-2.7 cm (10-cm VAS )/**20-27 mm** (100-mm VAS) |
| | Substantial improvement | **50%** |

OMERACT=Outcome Measures in Rheumatology Clinical Trials; MCID=minimal clinically important difference; OARSI=Osteoarthritis Research Society International; IMMPACT=the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.


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## Clinical relevance: *between-group* trial effect

| Source | Term Used | Definition |
|---|---|---|
| **IMMPACT (Dworkin 2009)** | Clinically important group difference | Always less than clinically important within-group (individual) improvement (adjustment for placebo effect).<br>No value specified.<br>Responder rates—better approach to analysis in trials. |
| **Rutjes review** | MCID, pain | Effect size (SMD), 0.37<br>(based on research suggesting ~1 cm on 10-cm VAS as minimal to moderate clinical improvement) |


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## Clinical relevance, KQ #1a findings: pain

- WMDs: 11.0 (**Bellamy 2006**) , 10.20 (**Colen 2012**) on 100-mm scales
  - Clinical response within groups or in individuals = 10-30
  - Between-group trial differences might be smaller, but no recognized threshold.
  - Bellamy conclusion: "HA is effective"
  - Colen conclusion: "Clinical relevance is debatable"
- SMD: 0.37 (**Rutjes 2012**)
  - Prespecified MCID for trial effect: 0.37 (equivalent to ~1-point difference on 10-cm VAS).
  - Conclusion emphasized clinically *irrelevan*t effect (0.11) in large trials with adequate assessor blinding


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## Clinical relevance, KQ #1a findings: physical function at 3 mos

- SMDs:
  - 0.9 (**Bellamy 2006**, 7 RCTs)
  - 0.33 (**Rutjes 2012**, 48 RCTs)
- No definitions of clinically relevant trial-based effect on physical function
- Rutjes et al. called the effect "moderate"
  - But emphasized the clinically *irrelevant* effect (0.09) in large trials with adequate assessor blinding.




## Findings, Key Question #1a: responder rates (vs placebo)

- 11 double-blind RCTs (4029 pts)
- Response (variable f/u intervals)
  - HA arms: 30%-81%
  - Placebo arms: 27%-68%
- Results favored HA, 9 RCTs (f/u 2 mos to 34 wks)
  - Absolute difference: 3-16 percentage points
  - NNT 7-16, depending on f/u
- Results favored placebo, 2 RCTs (f/u 3 mos)
  - Absolute difference:-2 to -3 percentage points

*Low quality:* Lack of or unclear statistical significance, some studies. Some inconsistency in direction of findings.

## Findings, Key Question #1a: responder rates (add-on to usual care)

- 2 pragmatic RCTs (761 pts)
- Response
  - HA arms: Pain 69%-88%; composite 31%-65%
  - Placebo arms: Pain 40%-68%; composite 14%-40%
- Absolute rate differences
  - 15-27 percentage points favoring HA
  - NNT values: 4-6
- All differences statistically significant
- *Moderate quality*: Good RCTs (except neither pt nor assessor blinding), consistent
- Publication dates 2002-2003, Canadian and French settings. Generalizability?
- Industry funding in 1 study; unclear in other


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## Findings, Key Question #1a: other

- Quality of life *(low quality)*
  - 6 fair-good RCTs (2147 pts)
  - 4 studies: No effect (no group difference)
  - 2 studies: Improvement in HA arms, no data for placebo arms
- Repeat course of injection *(low)*
  - 3 RCTs w/ high dropout rate between courses
  - Efficacy, 2nd course ≈ 1st
- Versus NSAIDs *(no quality rating)*
  - 4 RCTs in Bellamy review
  - HA≈NSAIDs (pain)
- Versus IACS *(low)*
  - Bannuru 2009 review; pain relief (7 RCTs, 606 pts)
  - IACS superior to HA up to 1 mo, then reverses
  - At 17-26 wks: SMD -0.39 (CI, 0.18-0.59); $I^2$=0 (favors HA)


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## Findings, Key Question #1a: recap

| Outcome *# Studies)* | Direction of Findings *(Quality of Evidence)* |
|---|---|
| **Pain** * *4 good SRs w/ MA + 1 RCT=81 RCTs total, >10,000 pts* | ↑ *(moderate)* |
| **Physical function*** *3 good SRs w/ MA)* | ↑ *(moderate)* |
| **Quality of life*** *6 fair-good RCTs, 2147 pts* | = *(moderate)* |
| **Repeat course*** *3 RCTs w/ high dropout)* | = *(low)* |

**Generally placebo-controlled trials (saline injection)*


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## Findings, Key Question #1a: preview (cont.)

| Outcome *# Studies* | Direction of Findings *(Quality of Evidence)* |
|---|---|
| **Responder rates** *11 placebo-controlled RCTs w/ deficiencies* | ↑ *(low)* |
| **Responder rates** *2 good pragmatic RCTs* | ↑ *(moderate , generalizability?)* |
| **Versus NSAIDs** *4 RCTs reviewed by Bellamy 2006* | = *(study quality not available)* |
| **Versus IACS** *1 fair-good SR, study quality poor* | HA longer lasting *(low)* |
| **Versus glucosamine and/or chondroitin** | ? *(no evidence)* |


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## Take-home message, clinical relevance

- Main pooled estimates = or slightly > SR authors' definitions of MCID.
- Rutjes 2012: In 18 larger RCTs with adequate assessor blinding, pooled estimates < MCID.


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## Findings, KQ #1b: hylan (Synvisc) vs non-cross-linked HA

- Small but NS pain effect favoring hylan
  - Reichenbach 2007: **SMD -0.27** (CI, -0.55 to 0.01); $I^2$=88% (13 comparator RCTs, 2085 pts). No effect w/o 2 outliers; MCID defined as -0.30.
  - Colen 2012: **SMD -0.07** (CI, -0.24 to 0.10); $I^2$=72% (12 comparator RCTs). Inconsistency across trials.
  - Rutjes 2012, subset (indirect) analysis: **SMD -0.53 vs -0.29** (*P*=0.099) (75 noncomparator RCTs, 9722 pts)
- Increased risk of adverse events
  - Reichenbach 2007: **RR=1.91** (CI, 1.04-3.49) (6 RCTs w/ consistent findings favoring non-cross-linked HA)

*Low quality:* Poor studies, inconsistency/imprecision


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## Findings, KQ #1b: efficacy by molecular weight

- Reichenbach 2007 (SR)
  - Metaregression, no association.
- Petrella 2011 (RCT):
  - High + low slightly superior to high or low alone ($P<0.001$).
  - NS difference favoring low molecular weight compared with high and low weight.

*Low quality:* Poor study quality, metaregression is indirect substitute for comparator trials.


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## Findings, Key Question #2: preview

| Outcome | Relative Risk, HA vs Control | Quality of Evidence |
|---|---|---|
| **Short-term safety**<br>Any event<br>Transient local adverse reactions<br>Serious (systemic) events, *but*<br>Risk difference <0.09%<br>Causal relationship unclear for most events | =<br>−<br>− | High |
| **Long-term safety**<br>Repeat course<br>Late events (>1 yr) | ? Mixed findings<br>? No data | Insufficient evidence |


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## Findings, KQ #2: any adverse event

- Bellamy 2006
  - 12 adverse events: No difference
  - Pain at injection site: RR=1.7 (95% CI, 1.19 to 2.44; *P*=0.004) (# RCTs NR)
- Rutjes 2012
  - All trials (25 RCTs, 5204 pts): **RR=1.04** (CI, 0.99–1.09); no heterogeneity
  - n=100/grp+adequate assessor blinding: RR=1.01 (CI, 0.96–1.06); no heterogeneity (11 RCTs, 3214 pts)
- Recent RCTs
  - Similar rates between HA and placebo.


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## Findings, KQ #2: any adverse event (cont.)

- Case series rates (f/u ≤2 wks after last injection)
  - Hylan (Synvisc)
    - **5.3%–8.3% of persons** (2 series, 4589 pts, mix of first-time and repeat courses of treatment)
    - **2.1%–2.7% of injections** (2 series, 5468 injections, mix of first-time and repeat courses of treatment)
  - Non-cross-linked HA
    - **0.8% of pts** (1 series, 1266 pts; some hip OA included)


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## Findings, KQ #2: local adverse event

- Rutjes review
  - Any: **RR=1.34** (CI, 1.13–1.60); no heterogeneity
  - Flares: RR=1.51 (significant)
  - Effusions: RR=1.15 (NS)
- Goldberg review and case report
  - 29 cases pseudosepsis
  - All but 1 following hylan injection, and typically after ≥ 2 injections within a course of treatment


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## Findings, KQ #2: serious adverse event

- Rutjes review
  - All trials w/ data): **RR=1.41** (CI, 1.02–1.97); no heterogeneity (14 RCTs, 3667 pts)
    - Serious events (n=35) included 10 gastrointestinal events (2 HA, 8 control), 7 cardiovascular events (5 HA, 2 control), 6 cases of cancer (6 HA, 0 control), and 6 cases of musculoskeletal disorders (4 HA, 2 control).
    - Crude overall rate (both arms included): **0.9%** (35/3667)
  - n=100/grp+adequate assessor blinding: RR=1.55 (CI, 1.07–2.24); no heterogeneity (11 RCTs)


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## Findings, KQ #2: serious adverse event (cont.)

- Individual RCT results
  - 22 RCTs w/ sample size ≥ 200 (overlap w/ 14 RCTs in Rutjes review)
  - No serious adverse events attributed to treatment
- Case series (follow-up ≤ 2 weeks)
  - 3 series described in Samson review
    - All involving hylan
    - 1 event (large effusion w/ synovitis)
  - 1 series (Foti 2011)
    - Hyalgan
    - **0.08% of pts** (pain or swelling at injection site, other)


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## Findings, KQ #2: other comparisons

- Versus NSAIDs (Bellamy 2006)
  - More local reactions but fewer systemic adverse events with HA.
- Versus usual care (2 pragmatic RCTs)
  - Raynauld 2002: All events, 52% vs 68% (*P*=0.0116); no serious events in HA arm.
  - Kahan 2003: All events, 44.2% vs 31.9% (significance NR); gastrointestinal events, 3.5% vs 11.9%; none serious.
- Incidence during 2nd course
  - ≈ incidence during 1st (2 RCTs; Euflexxa, Altman 2011; Gel-One; Strand 2012b).
  - Much higher per-person or per-injection during repeat course (2 case series, hylan).


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## Findings, Key Question #2: recap

| Outcome | Relative Risk, HA vs Control | Quality of Evidence |
|---|---|---|
| **Short-term safety**<br>Any event<br>Transient local adverse reactions<br>Serious (systemic) events, *but*<br>Risk difference <0.09%<br>Causal relationship unclear for most events | =<br>-<br>- | High |
| **Long-term safety**<br>Repeat course<br>Late events (>1 yr) | ? Mixed findings<br>? No data | Insufficient evidence |


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## Findings, KQ #3

- Greater benefit: Age ≤ 65 years, less severe OA (*low quality)*
  - 1 SR/MA (Wang 2004) (20 RCTs)
  - Magnitude of difference unknown
  - Outdated (substantial # missing RCTs)
- *Insufficient evidence*
  - Race/ethnicity
  - Gender
  - Primary versus secondary OA
  - Disease duration
  - Weight (body mass index)
  - Prior treatments


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# Findings, KQ #4

| Country<br>Perspective<br>Time Frame<br>Comparator | Results |
|---|---|
| **HA as add-on to usual care (pragmatic trial-based)** | |
| **Canada**<br>Societal<br>1-yr<br>Usual care alone<br>(hylan) | **CAD 10,000/QALY, 1999 costs**<br>(USD 11,273/QALY, 2013 dollars)<br>CAD 2505/QALY per patient improved, 1999 costs<br>(USD 2824/QALY, 2013 dollars)<br><br>(industry funding) |
| **France**<br>Societal<br>9 mos<br>Usual care alone?<br>(hylan) | **HA more effective** than usual care alone<br>**Comparable costs**<br><br>(unclear funding) |


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# Findings, KQ #4 (cont.)

| Country<br>Perspective<br>Time Frame<br>Comparator | Results |
|---|---|
| **HA vs placebo (modeling studies; costs from nontrial sources)** | |
| **Taiwan**<br>Societal<br>26 wks<br>NSAIDs (reference: no change in treatment) | HA vs naproxen, $33,148/QALY, 2001 costs<br>(USD 42,652, 2013 dollars)<br>Celecoxib vs naproxen, $21,226/QALY, 2001 costs<br>(USD 27,312, 2013 dollars)<br>**HA vs celecoxib, $42,000/QALY, 2001 costs**<br>(USD 54,042, 2013 dollars) |
| **UK**<br>National Health Service (NHS)<br>26 wks<br>Placebo (reference unstated) | 1 trial: cost-effectiveness ratio exceeded NHS threshold<br>Other trial: placebo both more effective and less expensive<br>No comparison of adverse effects<br>Products not available in the United States |


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# Findings, KQ #4: limitations

- Small # of studies
- May not apply to the U.S.
- More meaningful studies used hylan (Synvisc), >10 years old
- No data specific to single-injection treatments
- No data for HA vs IACS
- 3 studies: societal perspective (including productivity losses), not payer perspective


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# Practice guidelines

| Sponsor | Relevant Recommendations | Quality/Comments |
|---|---|---|
| **American Academy of Orthopaedic Surgeons (AAOS), 2013** | Cannot recommend for symptomatic OA of the knee. | Good (6 of possible 7)<br>Missing RCTs.<br>Conclusions consistent w/ SRs.<br>No apparent consideration of comparative safety. |
| **American College of Rheumatology (ACR), 2012** | No evidence-based recommendation possible. | Good (5 of possible 7)<br>Search ended December 2010. |
| **NICE, 2008** | Not recommended for OA. | Good (2010 rating, no numerical score) |
| **OARSI (2007-2010)** | May be useful in pts w/ OA of knee (level of evidence Ia, strength of recommendation 64% on 100-point VAS). | Good (6 of possible 7)<br>Possible corporate influence and somewhat outdated. |


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# Selected payer policies

| Payer | Policy |
|---|---|
| **Aetna** | Medically necessary for OA of knee when:<br>• Physical therapy and pharmacological treatment →no functional improvement after ≥ 3 months.<br>• Inadequate relief from IACS.<br><br>Additional series medically necessary after ≥ 3 months since last series if:<br>• Documented reduction in analgesics or anti-inflammatory medication during 3 mos following previous series.<br>• Documented improvement in pain and function. |
| **CMS** | No National Coverage Determination |
| **Regence** | No coverage policy, but medication policy requires prior authorization and limits coverage to 2 courses per year. |
| **Group Health** | Same as Regence. |
| **OR HERC** | Should not be covered for pain associated with OA of knee (HERC = Health Evidence Review Commission). |


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# Final summary: main findings

- Efficacy: Improved pain and function, peaking by 3 months.
  - Magnitude of placebo-adjusted benefit may be too small to be clinically important for many, if not most, patients.
- Effectiveness in practice: Some evidence of clinically meaningful benefit when added to usual care.
- Longer lasting than IACS (low quality), but no information on patients' past experience with IACS.
- Efficacy by molecular weight uncertain; hylan may be less safe.
- Increased risk of local reactions, but generally transient and not severe.
- Reduced risk of gastrointestinal events.
- Efficacy may be greater in pts ≤ 65 yrs of age and with less severe OA.
- Cost-effectiveness has not been studied in U.S. setting.


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## Gaps in the evidence

- Responder rates and economic evaluation in current, U.S. real-world practice.
- Efficacy/safety of different dosing regimens and repeat treatments.
- Comparison with glucosamine and/or chondroitin.
- Causal relationship between viscosupplementation and systemic adverse events.
- Long-term safety data.
- Differential effectiveness and safety by patient characteristics and previous treatment history.


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## Miller and Block, 2013 (not included in report)

- Published September 2013 in *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders*.
- Funded by HA Viscosupplementation Coalition (Bioventus, DePuy Synthes Mitek, Ferring, Fidia, Zimmer).
- SR with MA, 29 RCTs using FDA-approved products.
- Pooled estimates of between-group differences.
  - **Pain** at 4–13 wks: **SMD 0.43** (CI, 0.26–0.60; $P<0.001$)
  - Pain at 14–26 wks: SMD 0.38 (CI, 0.21–0.55; $P<0.001$)
  - **Function** at 4–13 wks: **SMD 0.34** (CI, 0.16–0.51; $P<0.001$)
  - Function at 14–26 wks: SMD 0.32 (CI, 0.18–0.45; $P<0.001$)
  - High heterogeneity: $I^2=74\%–92\%$; $P<0.001$
  - Evidence of publication bias for pain but not function
- **Rutjes review: SMD 0.37 for pain and SMD 0.33 for function.**
- No definition of clinical relevance/response, sensitivity analyses, or comparison with estimates derived from trials of non-FDA products.


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# 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 three 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-effective[1] 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

[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

[3] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

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.

## 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 evidence[4] 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 |

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

### *3. Factors for Consideration - Importance*

At the end of discussion a 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.

## Medicare Coverage and Guidelines

[from page 83 of evidence report]

***Centers for Medicare & Medicaid Services (CMS):*** No CMS National Coverage Determination (NCD) was identified for viscosupplementation on June 19, 2013 (search National Coverage Documents, National Coverage Determinations, by keywords *viscosupplementation, hyaluronic acid, hyaluronan, hyaluronate* and in entire document at: CMS Advanced Search Database). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

[from page 74 of evidence report]

# Practice Guidelines

The 4 guidelines selected for this update report were considered to be of good quality. Two organizations—the American College of Rheumatology (ACR) (Hochberg et al., 2012) and the American Academy of Orthopaedic Surgeons (AAOS) (AAOS, 2013)—have replaced the guidance described in the 2010 report with more negative recommendations regarding viscosupplementation for OA of the knee. Both organizations' guidelines referred to the incorporation of more formal methods into their guideline development processes since previous guidelines were issued; the AAOS also described the use of methodologists rather than clinicians to conduct the literature search and study appraisal. The National Institute for Health and Care Excellence (NICE) previously made a negative recommendation that has not been updated (NICE, 2008). Guidance issued by the Osteoarthritis Research Society International (OARSI) now provides an update literature review unavailable at the time of the 2010 report, but OARSI has not changed the previous positive although weak endorsement of viscosupplementation for knee OA (Zhang et al., 2007; Zhang et al., 2008; Zhang et al., 2010).

*American Academy of Orthopaedic Surgeons (AAOS)*

The American Academy of Orthopaedic Surgeons (AAOS) published a guideline on the treatment for OA of the knee that was rated as good quality (AAOS, 2008). The physician work group responsible for development of the guideline used an Agency for Healthcare Research and Quality (AHRQ) technology

assessment (Samson et al., 2007) as the evidence base for the recommendation pertaining to the use of intraarticular HA for treatment of OA of the knee. The authors of the guideline concluded that they could not recommend for or against the use of intraarticular HA as treatment for OA of the knee. This inconclusive rating was due to conflicting evidence in pooled effects from poor-quality trials relative to higher-quality trials, as well as unclear clinical significance of the results. There was no explicit consideration of comparative safety. The AHRQ report did not consider viscosupplementation versus conventional care or cost-effectiveness.

In 2013, revised guidelines on the treatment for OA of the knee were published (AAOS, 2013). These guidelines were also considered to be of good quality. In contrast to the 2008 guidelines, these guidelines were based on an analysis of primary studies only and did not consider secondary analyses such as published systematic reviews. Only studies published in full in peer-reviewed journals were eligible, and sample sizes had to include ≥ 30 participants in each treatment group. The work group selected 20 RCTs; some were placebo-controlled trials and others were comparisons of different HA formulations. A number of RCTs that would seem to meet the report's selection criteria are missing. Consistent with more inclusive systematic reviews, meta-analyses conducted by the guideline work group showed improvement in both pain (5 RCTs) and function (5 RCTs) to be statistically significant but considerably smaller than prespecified levels of minimum clinically important improvement (MCII). The reported analyses were not specific to a particular follow-up interval, but study selection criteria required a follow-up of ≥ 4 weeks. The guideline authors prespecified definition of MCID was an effect size of 0.39 and was based on some of the same research serving as the basis of the MCID used in the Rutjes review. The final conclusion was that the work group could *not* recommend using hyaluronic acid for patients with symptomatic OA of the knee, and the recommendation was characterized as *strong.* No harms analysis was conducted. There was also no analysis of viscosupplementation as an add-on treatment to usual care alone and no cost-effectiveness analysis.

*American College of Rheumatology (ACR)*

New guidelines, *Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee*, were published by the ACR in 2012 (Hochberg et al., 2012). The new guidelines were based on a systematic search of the literature extending through December 2010. For each modality and indication, the best available systematic review, meta-analysis, or RCT was selected. The guidelines for knee OA are predicated on the following base case:

> An adult with symptomatic knee OA without cardiovascular comorbidities, current or past upper GI problems, or chronic kidney disease presents to her primary care provider for treatment. She experiences pain in and/or around her knee(s) and has not had an adequate response to either intermittent dosing of OTC (over-the-counter) acetaminophen, OTC NSAIDs, or OTC nutritional supplements (e.g., chondroitin sulfate, glucosamine (Hochberg et al., p. 469).

The guidelines panel concluded that it could make *no recommendation r*egarding the use of intraarticular hyaluronates. This represents a substantial modification of the guidance issued in 2000, which suggested that intraarticular hyaluronan therapy is indicated for use in patients who have not responded to a program of nonpharmacological therapy and simple analgesics (ACR, 2000). In addition to the main statement about HA, the 2012 document *conditionally* recommends the use of tramadol, duloxetine, or intraarticular HA in lieu of oral NSAIDs for elderly individuals (≥ 75 years of age). Conditional recommendations apply to treatments that most but not all informed patients would be expected to choose. No evidence was cited for the conditional recommendation. The guideline document further advises that oral NSAIDs should not be used in patients with advanced chronic kidney disease; no statement about HA injections in this population is made (Hochberg et al., 2012).

*National Institute for Health and Care Excellence (formerly National Institute for Health and Clinical Excellence) (NICE)*

The NICE guideline covers the care and management of OA in adults (NICE, 2008). The quality of this guideline was rated as good. The authors note that the evidence suggests that intraarticular hyaluronan may provide a treatment benefit for pain reduction up to 3 months after a series of 3 to 5 injections, but with a generally small effect size. A limited cost-effectiveness analysis led to the conclusion that hyaluronans are not within the realm of affordability. The guidance from NICE states that intraarticular hyaluronan injections are not recommended for the treatment of OA.

*Osteoarthritis Research Society International (OARSI)*

The 2007 and 2008 versions of OARSI guidelines on management of hip and knee OA (Zhang et al., 2007, 2008) were reviewed in the 2010 report. Those guidelines provided a critical evaluation of existing systematic reviews and treatment guidelines (published from 1945 to October 2005) and a systematic review of research evidence from recent studies (up to January 2006). One specific recommendation pertaining to viscosupplementation was issued: that injection of intraarticular hyaluronate may be useful in patients with OA of the knee (level of evidence Ia, strength of recommendation 64% on a 100-point VAS). The authors noted that these injections are characterized by delayed onset, but prolonged duration, of treatment benefit compared with intraarticular injections of corticosteroids. The 2008 guidelines cited the meta-analyses by Lo et al. (2003) and Arrich et al. (2005) (both included in the Samson review) as evidence. Zhang and colleagues report a pooled estimate of the effect size for pain at 2 to 3 months as 0.32 (CI, 0.17 to 0.47). It is not clear how this pooled estimate was derived.

The 2010 guidelines (Zhang et al., 2010), which focused on literature published from January 31, 2006 to January 31, 2009, selected the Cochrane review (Bellamy et al., 2006) on the basis of quality and comprehensiveness as the most representative new evidence for the efficacy of viscosupplementation for knee OA. This document assigns a level of evidence of Ia to the Bellamy review and does not provide a revised overall statement about viscosupplementation. The authors cite the findings of Reichenbach et al. (2007) (no significant difference between hylan and standard HA) and Bannuru et al. (2009) (superior durability of effect, comparing HA with corticosteroid injection) but otherwise do not add to the recommendation stated in 2008. An updated pooled estimate for effect size regarding pain is reported: 0.60 (CI, 0.37 to 0.83). Again, the methods for deriving that estimate are not described.

The OARSI guidelines were considered to be of good quality in terms of rigor of development but the organization includes corporate members, and most of the guideline authors, other than the lead author, had financial ties to manufacturers of HA products. The corporate influence on conclusions was unclear.

## HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

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

| Safety Outcomes | Safety Evidence |
|---|---|
| Transient local adverse reaction | |
| Systemic events | |
| Pain or swelling @ injection site | |
| | |
| | |
| | |
| | |
| **Efficacy – Effectiveness Outcomes** | **Efficacy / Effectiveness Evidence** |
| Pain | |
| Physical Function | |
| Quality of Life | |
| Repeat course | |
| | |
| | |
| | |
| | |
| **Special Population / Considerations Outcomes** | **Special Population Evidence** |
| Age | |
| Race/ethnicity | |
| Gender | |
| OA severity | |

| | |
|---|---|
| Disease duration | |
| BMI | |
| Prior treatments | |
| **Cost** | **Cost Evidence** |
| Direct cost, product/procedure | |
| 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?