



**Washington State
Health Care Authority**

Health Technology Assessment Program

**Health Technology Clinical Committee
August 2009 Meeting**

Bone Growth Stimulators (BGS) Topic

- Brief Background Relevant to Policy Issues
 - Disease and Diagnosis
 - Treatments
 - Selected Technology
- Agency Prioritization Criteria and Concerns
- Medicare Coverage Decision
- Treatment Guidelines

Topic Background: Disease/Diagnosis

- Bone fractures are a common musculoskeletal injury with 7.9 million occurring in the US annually.
- Majority of fractures heal without complications following standard nonsurgical or surgical therapy, healing is delayed or impaired in 5% to 10% of cases.
 - Delayed healing is associated with longer recovery, reduction in quality of life and function, and pain
 - There is no standard definition of nonunion; FDA considers a nonunion to be established “when a minimum of 9 months has elapsed since injury and the fracture site shows no visibly progressive signs of healing for minimum of 3 months.”
 - There are variations in the clinical and radiographic findings used to diagnose nonunion
- Bone union is also a potential concern in patients who undergo joint fusion surgery and in patients with fresh fractures who are at risk of delayed or nonunion
 - Lifestyle modification (smoking, obesity, alcoholism) and infection control are important

- Bone Growth Stimulators (BGS)
 - Clinical theory: bone healing requires stability and blood supply. Clinical studies demonstrate that bone healing is associated with electrical potentials (appropriate blood flow) at the site.
 - BGS attempts to harness the electrical–biological link through the use of applied electrical fields to promote healing but link between biophysical stimulation and the cellular responses is not fully understood
 - BGS uses either electrical stimulation or low intensity pulsed ultrasound to induce bone growth and promote fracture healing. Invasive BGS are surgically implanted; non-invasive or worn externally
 - BGS are used as an adjunctive treatment with other fracture healing treatments including immobilization; surgical techniques; bone grafts; treatment of infection or other causes of non-union; and orthobiologics.

■ **Safety concern: Low**

- Primary safety concerns: non-invasive little risk concern; Implantable BGS – concern regarding device implantation risk

■ **Efficacy concern: High**

- Primary concern: low quality evidence currently available for most uses; adjunct treatment confounds results; patient selection and stimulation parameters (high dose; low doses; length of treatment and duration) unclear; patient compliance problematic.

■ **Cost Concern: Medium**

- Cost concerns reflect mainly concern about over or mis-utilization; expansion to other treatment areas, and cost of additional (not replacement) treatment

■ Key Question Function

- Sets parameters for research inquiry and policy decision

■ Key Question Components

- Legislatively, key questions are centered on a technology's evidence of safety, efficacy, effectiveness, and cost and application in any special population
- Methodologically, questions are refined to include a defined population, intervention, comparator(s), and outcome (PICO)

■ Bone Growth Stimulation Focus

- The overall question related to BGS is:
 - Are BGS effective in promoting healing, reducing pain, or improving function when applied to fresh fractures, delayed union or nonunion fractures, or fusion sites?
 - Are BGS safe?
 - Does effectiveness vary by type of bone, the presence/absence of comorbidities or other patient characteristics?

Medicare Coverage and Clinical Guidelines

- There is a National Medicare policy on BGS (p.15: MCD 150.2):
 - Electrical noninvasive and invasive stimulator device is covered only for the following indications:
 - Nonunion of long bone fractures (3 or more months ceased healing, 2 radiographs min. 90 days apart);
 - Failed fusion, where a minimum of 9 months has elapsed since the last surgery; or adjunct to fusion for patients with a previously failed fusion and high risk of psuedarthrosis
 - Congenital pseudarthroses (noninvasive only)
 - Ultrasonic stimulator
 - Nonunion confirmed by 2 radiographs min. 90 days apart and physician statement of no clinical evidence of fracture healing
 - Non covered indications –
 - Nonunion of skull, vertebrae or tumor related
 - Ultrasonic stimulator – fresh, delayed fractures and concurrent use with other noninvasive stimulator

Clinical Guidelines

- Guidelines begin on Page 79 of report
- BGS: AANS/CNS- Guideline regarding BGS and lumbar fusion (2009)
 - Treatment Standard: Insufficient evidence
 - Treatment guideline: electrical stimulation recommended as an adjunct to spinal fusion for patients at high risk for arthrodesis; PMEF stimulation recommended as adjunct to increase fusion rates in similar patients treated with lumbar interbody fusion procedures
- AHRQ Evidence review for CMS (2005)
 - Overall evidence quality low; treatment effect of device could not be distinguished from possible therapeutic effects of concurrent treatments
 - Randomized trials to separate possible

Questions?

Combined Magnetic Fields for Stimulation of Bone Repair: Biochemical Mechanisms and Clinical Applications in Nonunion Fracture Management and Spine Fusion

James T. Ryaby, Ph.D.

Consultant to DJO

Former SVP R & D; OrthoLogic Corp

Adjunct Professor of Bioengineering,
Arizona State University, Tempe, AZ

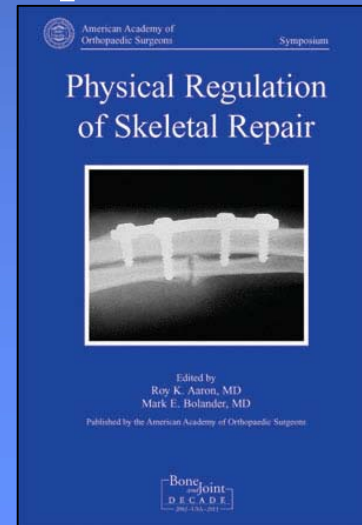
BGS Acceptance in the International Orthopedic Community Evidenced by:

AAOS – NIH Consensus Workshop “Physical Stimulation of Bone Repair”

Roy Aaron, MD – Brown University

Mark Bolander, MD – Mayo Clinic

Book published by AAOS (www.aaos.org) in 2005

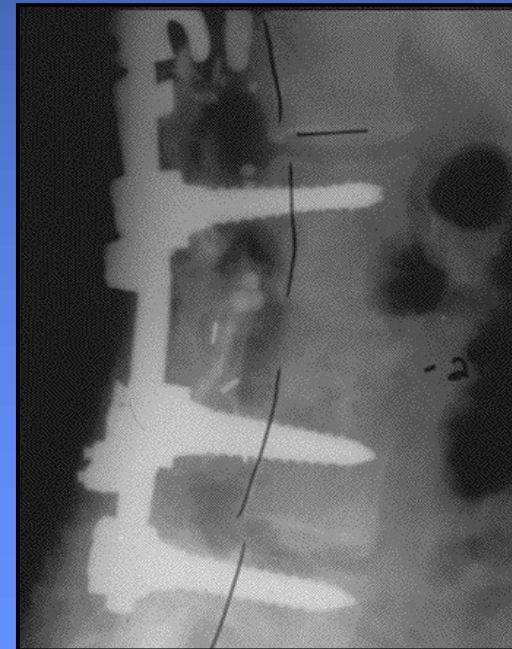


Noninvasive EMF for Adjunctive Stimulation of Spine Fusion Level One Evidence

Trial Design: Comparison of BGS to Gold Standard for Fusion - Autograft

**Prospective, Double Blind, Randomized,
Placebo Controlled Clinical Trials**

- Mooney (1990) - PEMF
- Goodwin et al. (1999) - CCEF
- Linovitz et al. (2000) - CMF

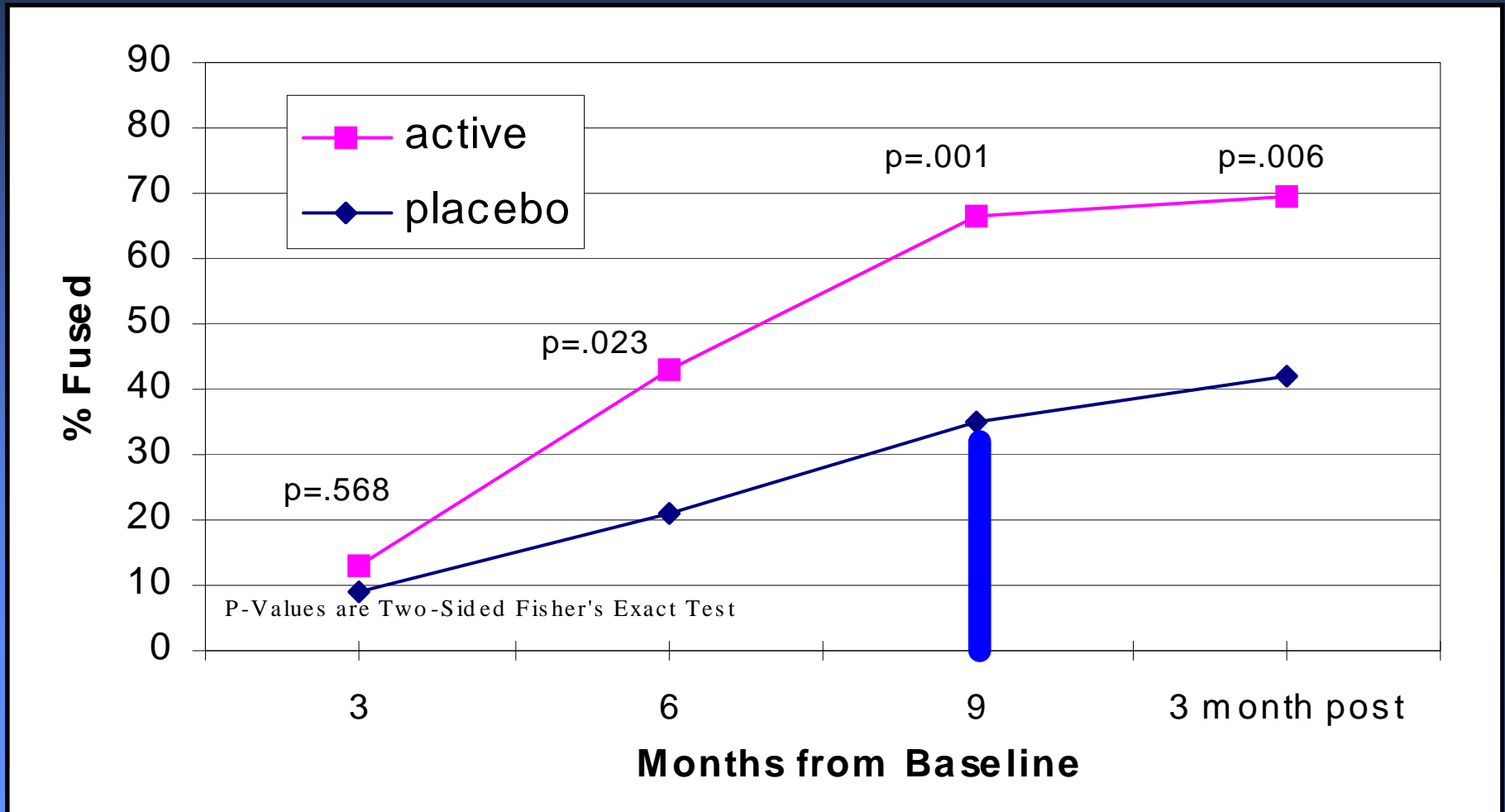


DJO SpinaLogic Technology

Linovitz, Ryaby, Garfin et al. (2002) *Spine* 27:1383-1389

- Prospective, double blind, randomized, placebo controlled
- Multicenter : 243 patients / 10 centers
- Rigorous Inclusion Criteria :
 - Posterolateral fusions only using autograft
 - No instrumentation
 - Autograft +/- allograft
- Follow-up every 3 months to one year
- Blinded radiographic review panel

Results – Female Study Subjects



DJO CMF Nonunion Technology FDA-approved Registry Data

- Prospective, Open label Clinical Trial
 - > 9 months post-injury
 - No surgery for prior 3 months
 - Blinded radiographic review
- Post PMA Approval Registry Data
 - Over 2300 patients in USA

CMF Registry Data

By Site (Efficacy)	Healed #/Total # n/N	Outcome Rates	Average Healing Time (months)
ANKLE	110/145	75.9%	4.7
CARPAL NAVICULAR	154/218	70.6%	3.9
CARPAL/ METACARPAL	35/39	89.7%	5.3
CLAVICLE	79/114	69.3%	5.1
FEMUR	160/250	64.0%	6.4
FIBULA	58/68	85.3%	4.3
HUMERUS	103/180	57.2%	5.5
METATARSAL	408/477	85.5%	3.8
PHALANX (FINGER)	21/24	87.5%	3.4
PHALANX (TOE)	22/29	75.9%	3.7
RADIUS	81/96	84.4%	5.0
RADIUS/ULNA	14/17	82.4%	5.3
TARSAL	51/77	66.2%	4.3
TIBIA	285/372	76.6%	6.2
TIBIA/FIBULA	122/154	79.2%	5.8
ULNA	77/110	70.0%	5.0

1780/2370

75.1%

4.9

Summary

- BGS technology rigorously evaluated in prospective clinical trials
- Level one evidence based on randomized, placebo controlled trials in spine fusion
- DJO CMF technology first to show scientific mechanism based on growth factors

Pulsed Electromagnetic Bone Growth Stimulation

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Assistant Professor of Neurosurgery

Department of Neurosurgery

Mayo Clinic Arizona

Naresh P. Patel MD

- **Board Certified Neurosurgeon**
- **BA: Cornell University, Ithaca, NY**
- **MD: Baylor College of Medicine, Houston, TX**
- **Neurosurgical Residency: Mount Sinai Medical Center, NYC, NY**
- **Spine Fellowship: UCLA Medical Center and Cedar-Sinai Medical Center, Los Angeles, CA**
- **Assistant Professor of Neurosurgery and Co-Director of Spine Surgery at the Mayo Clinic Arizona**
- **CV available on request; author of more than 100 peer-reviewed papers, book chapters, abstracts and presentations in the field of neurosurgery.**

Disclosure

- **Orthofix, Inc.**
 - **Reimbursement for time and travel today**
- **I have not received any of the following:**
 - **salary, royalties, intellectual property rights, research or educational grants, ownership interest (i.e., stocks, stock options) or any other financial benefit.**

Topics

- **Spine fusions – improving success rates**
- **Why Bone Growth Stimulation?**
- **Personal Experience and Clinical Evidence**

The Challenge of Failed Spine Fusion

- **Pseudoarthrosis (failed fusion) rates¹**
 - 10%-15% with instrumentation
 - 10%-40% without instrumentation
- **Revisions more difficult than primary**
- **67% of patients have one or more risk factors²**

Risk Factors

- **Smokers/tobacco use (23.8% of population)**
 - **Smokers: up to 40% pseudoarthrosis rate**
- **Diabetes (7.8% of pop.)**
- **Osteoporosis**
 - **1 in 3 women, 1 in 12 men over age 50**
 - **10 million Americans**
- **Obesity (26% of pop.)**
- **Multi-level fusions**
 - **20% -30% decrease in healing per level**
- **Revision procedures**
- **Allograft vs. Autograft (the “gold standard”)**
- **Spondylolisthesis (Grade 3+)**

Ways to Increase Fusion Success

- Proper patient selection
- Surgical technique/surgeon skill
- **Biologics¹ -- Bone Morphogenetic Protein (BMP)**
 - BMP used in 25% of spinal fusions (37% of revisions)
 - Adds ~\$15,000 to inpatient hospital bill
 - Complications: ectopic bone formation, edema, wound breakdown
 - Marked increase complication rate in ACDF: dysphagia, hoarseness of voice, airway obstruction, death
- **Electrical stimulation²**
 - Used in 21% of cases currently
 - ~\$3,200 in DME costs (national average)
 - No short-term or long-term risks

¹Cahill, K, MD, et al. Prevalence, Complications, and Hospital Charges Associated with Use of Bone-Morphogenetic Proteins in Spinal Fusion Procedures, JAMA. 2009;302:58-66

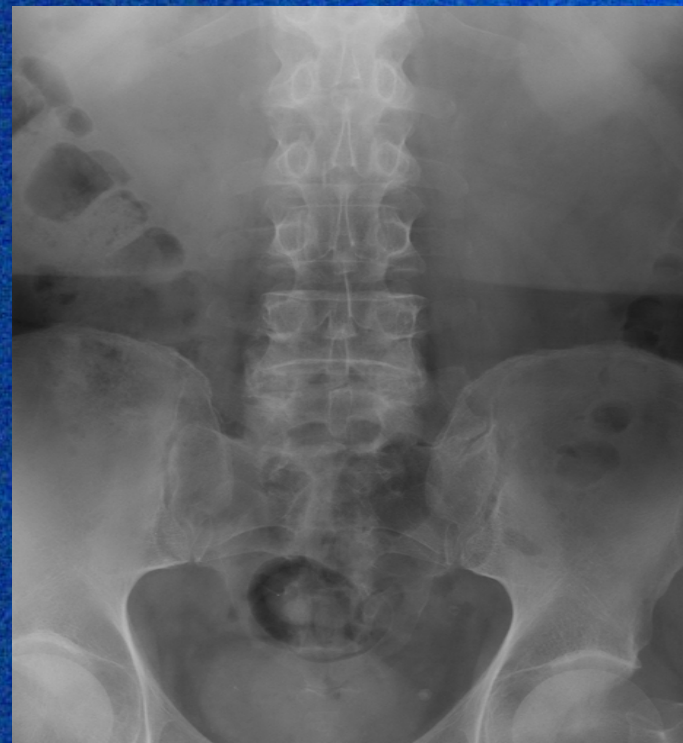
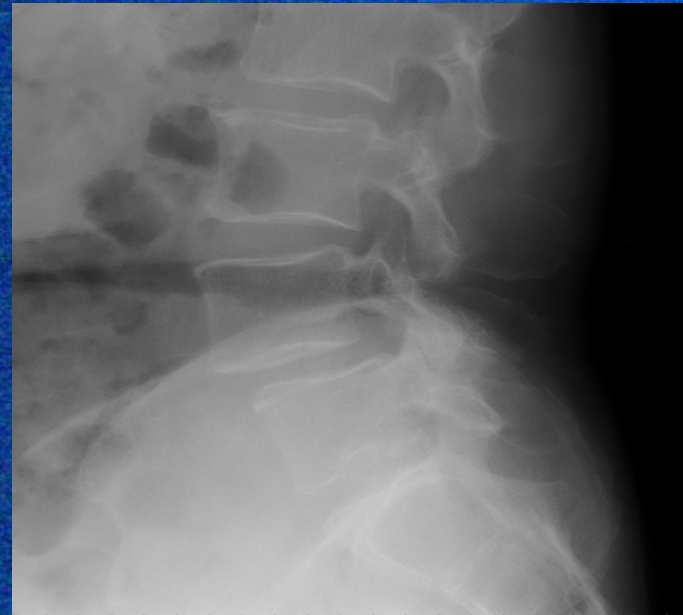
²iData Research Inc. 2009

Personal Experience with External Bone Growth Stimulators

- 2001-2009: 452 high risk spinal fusion procedures
- Risk Factors:
 - Tobacco use
 - Diabetes
 - Osteoporosis
 - Multilevel fusion
 - Revision surgery
- Follow-up at two weeks, three months, and one year.
- Plain x-rays/ Flexion & Extension/ Multiplanar CT
- Results: 427 fusions, 28 pseudoarthroses
- **94.5% fusion rate**

Case illustration

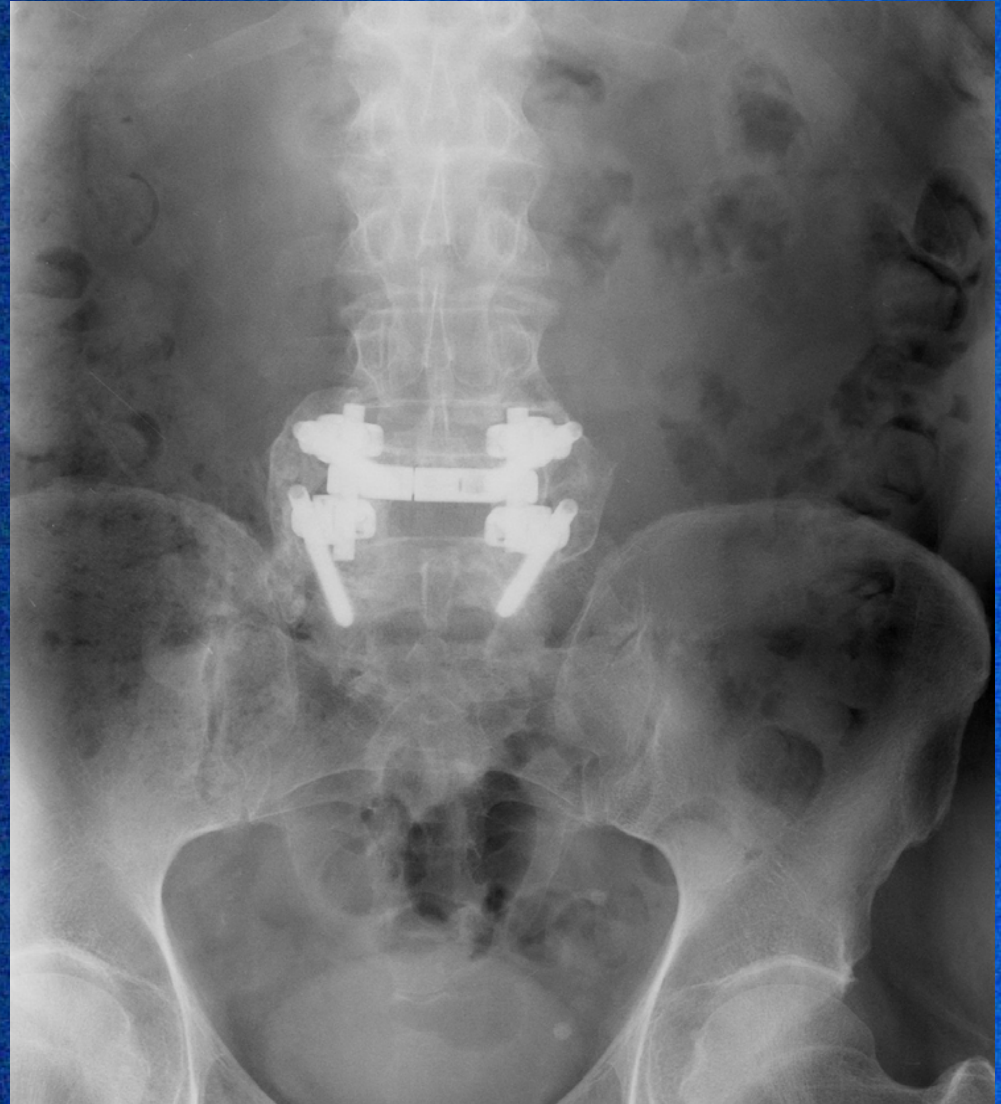
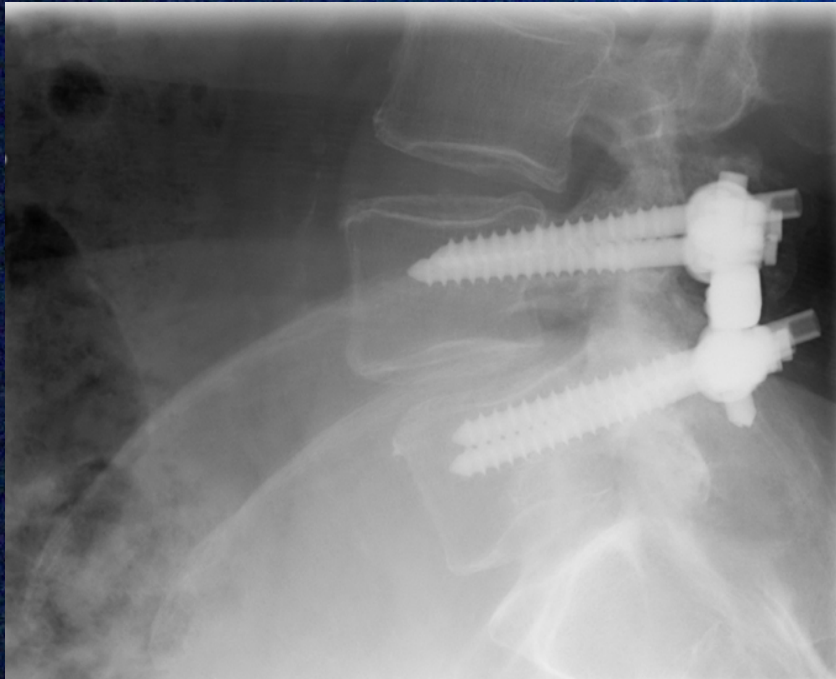
- 71 year old air conditioning repairman
 - Grade I L4-5 spondylolisthesis
 - Severe back and leg pain
 - Focal stenosis
- Insulin dependent diabetes
- 1 pack per day smoker x 35 years
- Failed non-operative therapy
 - Oral medications
 - Physical Therapy
 - Injections



Case illustration

L4-5 Instrumented Fusion

- Bone growth stimulator started within 2 weeks of surgery
- 6 month post-op films



PEMF Device Clinical Evidence (PMA Data Submitted to FDA)

Author	Type	Pub/Date	# Patients	Success Rate
Mooney	Prospective, Lumbar	Spine, 1990 Surgical Tech Int'l, 1993	195 patients (lumbar)	92% vs 67% ($p < 0.001$)
Simmons	Prospective, Non- randomized Lumbar	American Journal of Orthopedics, 2004	100 failed lumbar fusion (patients acted as own control)	67%
Foley	Prospective, randomized, Cervical	The Spine Journal, 2008	240 high risk (cervical)	84% vs 68% ($p = 0.0065$ @ 6- month endpoint)

Clinical Evidence: PEMF Device Publications

Author	Type	Pub/Date	# Patients	Success Rate
Silver	Retrospective	J. Neurological and Orthop Med & Surgery, 2000	85 total (66 high risk)	97.7%
Marks	Retrospective, Randomized	Advances in Therapy, Mar/Apr 2000	61 PEMF 19 Control	97.6% vs. 52.6% ($p < 0.001$)
Bose	Prospective	Advances in Therapy, Jan/Feb 2001	48 high risk No control	97.9% fused, 59% back to work

Summary

- **External Bone Growth Stimulation promotes spinal fusion in high risk patients.**
- **It is a well tolerated, safe adjunct without side effects or unintended consequences.**
- **Our clinical experience with the use of external PEMF stimulation has been extremely favorable with excellent fusion rates in difficult cases.**

Mark C. Olson, M.D.



Medical Interests

Fracture and Trauma Care
Arthroscopy
Hip, knee arthritis
Pediatric Orthopaedics
General Orthopaedics

Hospitals

Sacred Heart Medical Center
Deaconess Medical Center
Valley Hospital & Medical Center

Professional Memberships

-American Academy of
Orthopaedic Surgeons
-Spokane County Medical
Society
-Washington State Medical
Association
-Washington State
Orthopedic Association

Professional Activities

-American Academy of
Orthopaedic Surgeons
• Board of Counselors
• Aging Committee
-Chairman, Blood
Management Program,
Sacred Heart Medical Center
-Chairman, Orthopaedic
Service Dept., Sacred Heart
Medical Center 1996-2002



**WHY
PEMF?**

Non-Union

- What does non-union mean to the patient?
 - Metal Breakage
 - Pain
 - Decreased use of extremity
 - Alteration of daily activities/work

Options for the Patient

- Wait
- Operate
- **External Stimulation**

Option Overview

<u>Options</u>	<u>Risk</u>	<u>Cost</u>	<u>Life Modification</u>	<u>Time to Heal</u>
Wait	1	0	6-8	10
Operate	6-8	10	Short term- 9 Long term- 0-1	2
External Stimulation	0	4-5	3-4	5-6

Scale
Low-high
0-10

Bone Graft

- Expose the Non-Union
 - Hardware removal/Exchange/Leave/Add
 - Take bone graft- pelvis/long bone
-
- + Surgeon cost
 - + Hospital cost
 - + Increase of medication for the patient

Case Study

Before



- 52 YO Female smoker
History of alcoholism

- Right tibial shaft Fx

- DOI 5/22/07

- Six months no signs of healing

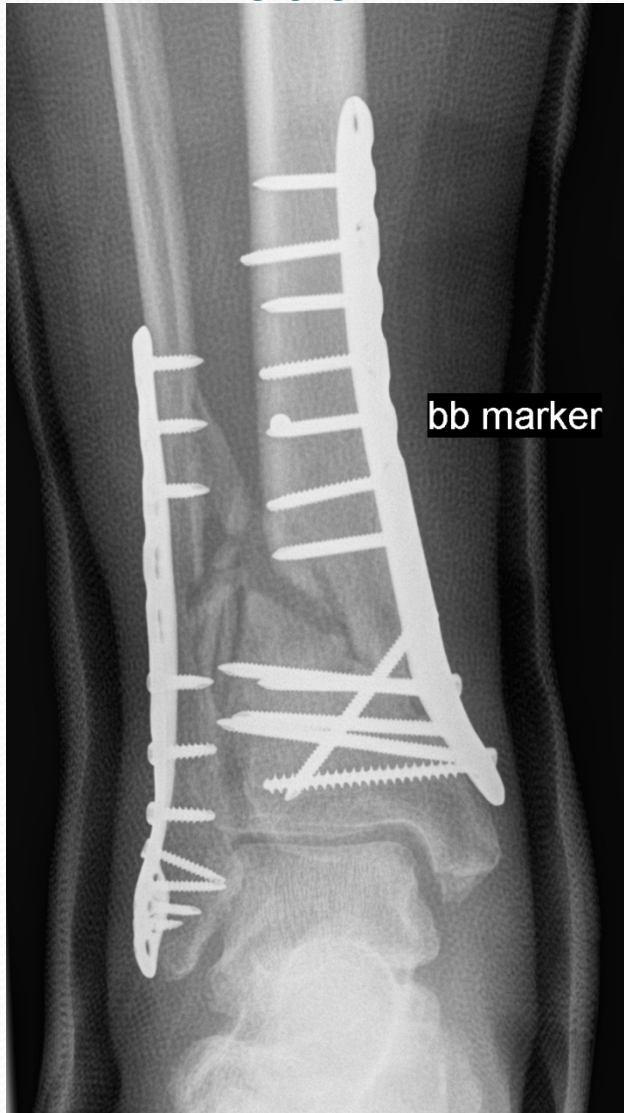
- Prescribed BGS
11/13/07

After



Case Study

Before



- 62 YO Male
- Distal Tib/Fib Fx
- DOI 2/24/09
- No signs of healing
3 ½ months
- Prescribed BGS
6/10/09

After



EXOGEN- Low Intensity Pulsed Ultrasound

Barbara Rohan, VP Government Affairs,
Smith & Nephew

- Is Exogen effective?
- Is Exogen safe?
- Is there different efficacy by patient type?

Evidence-Based Medicine

Where Does Ultrasound Fit In?

Mohit Bhandari MD, FRCSC

Canada Research Chair,
CLARITY Research Group,
Orthopaedic Trauma Service
McMaster University



Disclosure

- **Smith and Nephew**
 - Consultant
 - Research Funding: TRUST Trial (Industry-Partnered Grant)
 - No stock options, No Royalties, No non-competing clauses in our funding agreements

Hierarchy of Evidence

Meta-analysis



CMAJ • JAMC

February 19, 2002, Vol. 166, No. 4 • Le 19 février 2002, Vol. 166, n^o 4

www.cma.ca/cmaj

RESEARCH • RECHERCHE

The declining comprehensiveness of primary care

B.T.B. Chan

429

The effect of low-intensity pulsed ultrasound therapy
on time to fracture healing: a meta-analysis

J.W. Busse, M. Bbandari, A.V. Kulkarni, E. Tunks

437



Pooled Studies

Fracture Location	Samp. Size	Time to Heal -US	Time to Heal -Cont	Effect Size
Scaphoid	30	43 ± 11 days	62 ± 19 days	1.2
Distal Radius	61	61 ± 3 days	98 ± 5 days	8.8
Tibial Shaft	67	114 ± 7.5 days	182 ± 15.8 days	5.4

Fresh Fracture Bottom Line

- The weighted average effect size was 6.41 (95% confidence interval, 1.01-11.81).



- Ultrasound healed fractures faster:
Mean difference of 64 days
- 52% of surveyed orthopedic surgeons believe reduction in fx healing time of 4 weeks clinically significant
- The pooled reduction in radiographic healing time **37%** (95% CI = 26%-46%)

Nonunion Study Guidance

- FDA guidelines for bone growth stimulator clinical trial design:
- “In a clinical trial to evaluate the efficacy of a BGS device for treating established non-union fractures, **the patient can serve as his/her own control.** The assumptions underlying this approach are that:
 - at **nine months or more post injury**, other conventional therapies already would have been attempted and proven unsuccessful for this patient,
 - there has been **no evidence of progression in healing**; that is, no radiographic signs of callus formation, and
 - there have been **no intervening surgical procedures within the three-month period** immediately preceding device use.”

Exogen FDA Nonunion Study Design

- FDA approved nonunion study design:
 - Self-paired controls per FDA guidance
 - Inclusion of nonunion fractures that would not otherwise heal (9 months since fracture, 3 months since last intervention)
 - **Only treatment change was once daily use of Exogen device**
 - Ethics committee approval and oversight
 - Informed patient consent was obtained.

- 3 separate studies:
 - **Conducted at multiple centers**
 - **Pragmatic “real-world” experience**
 - **Clinical and radiographic evidence of healing**
 - **Data underwent detailed scrutiny by FDA inspectors**

Body of Evidence Demonstrates LIPUS can Resolve Nonunions without Surgery

Only treatment change was once daily use of Exogen device

Literature	Bone investigated	Fracture management	Patient Numbers	Fracture Heal Rate
Romano et al (1999)	Tibia, Humerus, Femur	Surgical	N=11	82%
Nolte et al (2001)	Scaphoid, Malleolus, Clavicle, Humerus, Femur, Radius / Ulna, Tibia / Fibula, Metatarsal	Conservative, Intramedullary nail , External fixation	N=29	86%
Mayr et al (2002)	Tibia /Fibula, Femur, Radius /ulna, Humerus, Clavicle, Scaphoid	Conservative, Intramedullary nail , External fixation	N=100	86%
Pigozzi et al (2004)	Scaphoid, Talar dome, Clavicle, Malleolus, Femur, Tibia	Conservative	N=15	100%
Lerner et al (2004)	Femur, Tibia, Radius/Ulna, Humerus	External fixation, Intramedullary nail	N=18	89%
Gebauer et al (2005)	Tibia/Fibula, Femur, Radius /ulna, Humerus, Metatarsal, Scaphoid	Conservative, Internal fixation, External fixation, surgical	N=67	85%
Jingushi et al (2007)	Femur, Tibia, Humerus, Radius, Ulna	Conservative, Intramedullary nail , External fixation	N=72	75%

Nonunion Summary

- Relatively small studies but consistent results across all patient types
- By definition patients will not spontaneously heal
 - Pragmatic and ethical issues with “gold standard” nonunion studies
- Despite a lack of Level I evidence, prospective studies provide sufficient evidence to guide patient care
- Future studies are needed to confirm (or refute) the findings of the cohorts published to date
- Less costly from societal perspective

Radiologic healing is accelerated but how does this relate to functional outcomes?

BMJ

RESEARCH

Low intensity pulsed ultrasonography for fractures: systematic review of randomised controlled trials

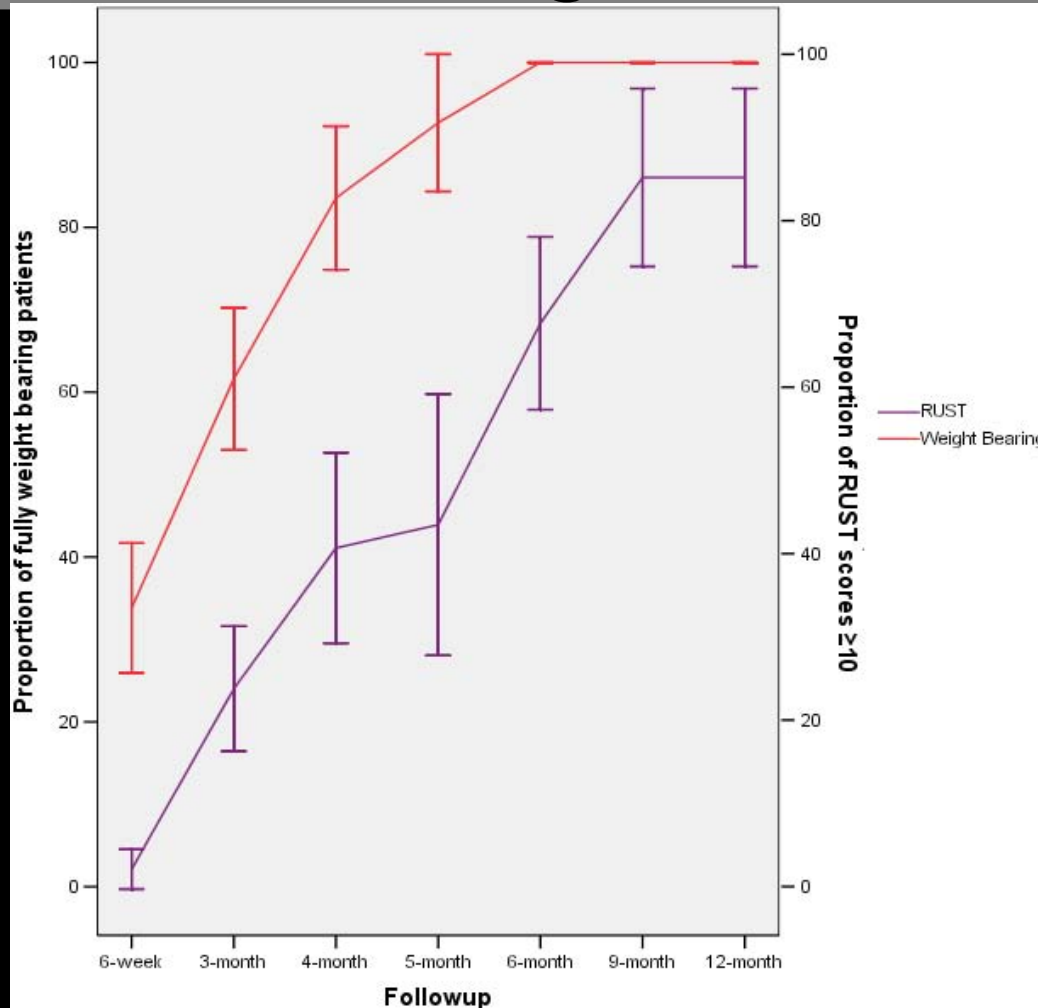
Jason W Busse, scientist, assistant professor,^{1,2} Jagdeep Kaur, student,² Brent Mollon, student,³ Mohit Bhandari, associate professor,² Paul Tormetta third, professor,⁴ Holger J Schünemann, professor,⁵ Gordon H Guyatt, professor²

Early Xray Healing May be a Good Surrogate for Function

Measure	Score	SF36-PF (mean)	SF36-RP (mean)	Full weight bearing (%)
Xray Score	4	25.7	12.0	21.7
	5	37.0	27.8	38.6
	6	42.8	32.4	66.5
	7	40.4	21.2	60.9
	8	44.5	28.2	64.8
	9	50.7	30.8	86.8
	10	58.4	39.3	89.7
	11	61.9	48.6	94.5
	12	67.6	56.5	100.0

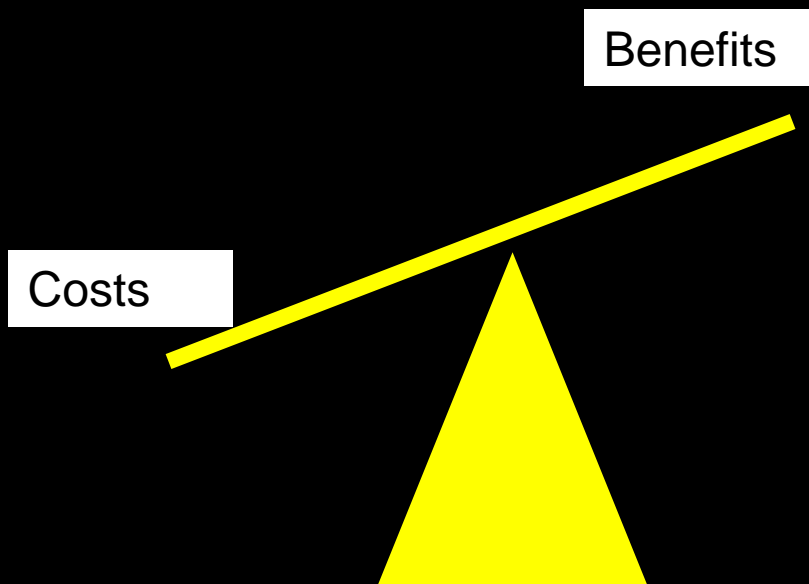
Xray Healing May Be a Good Surrogate for Function

%Full Wt Bearing



Time

Is the Use of Ultrasound Cost-Effective?



An Economic Analysis of Management Strategies for Closed and Open Grade I Tibial Shaft Fractures

Busse J, Bhandari M, Sprague S, Johnson-Masotti A, Gafni A

Acta Orthop Scandinavica

How do costs compare for

[1] operative treatment

[2] casting

[3] casting with ultrasound

Costs & Treatment Decisions

Societal Perspective

- Reamed IM Nail \$12 449
 - **Casting with Ultrasound** \$13 266
 - Non-Reamed Nail \$15 571
 - Casting alone \$17 343
-
- In tibial shaft fractures
 - **1st Choice:** Reamed IM Nail
 - **2nd Choice:** Casting with US

Cost Savings

- If we add Ultrasound to every casted fresh fractured Tibia:
 - We SAVE: **1.2 Billion Dollars**
- If we treat all tibial nonunions with adjunctive Ultrasound
 - We SAVE: **200 Million Dollars**

Thank You

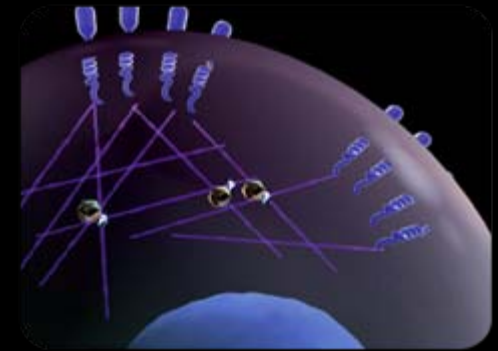
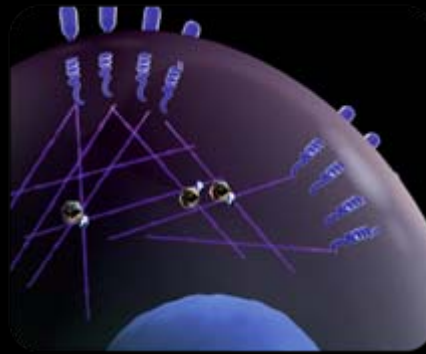
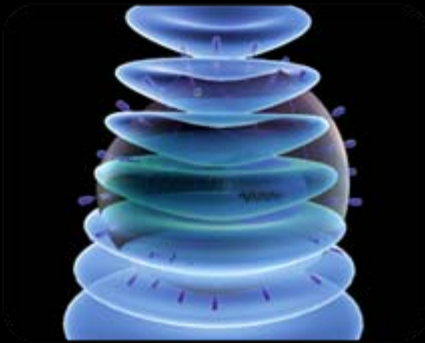


Mechanism of Action

Neill Pounder, PhD

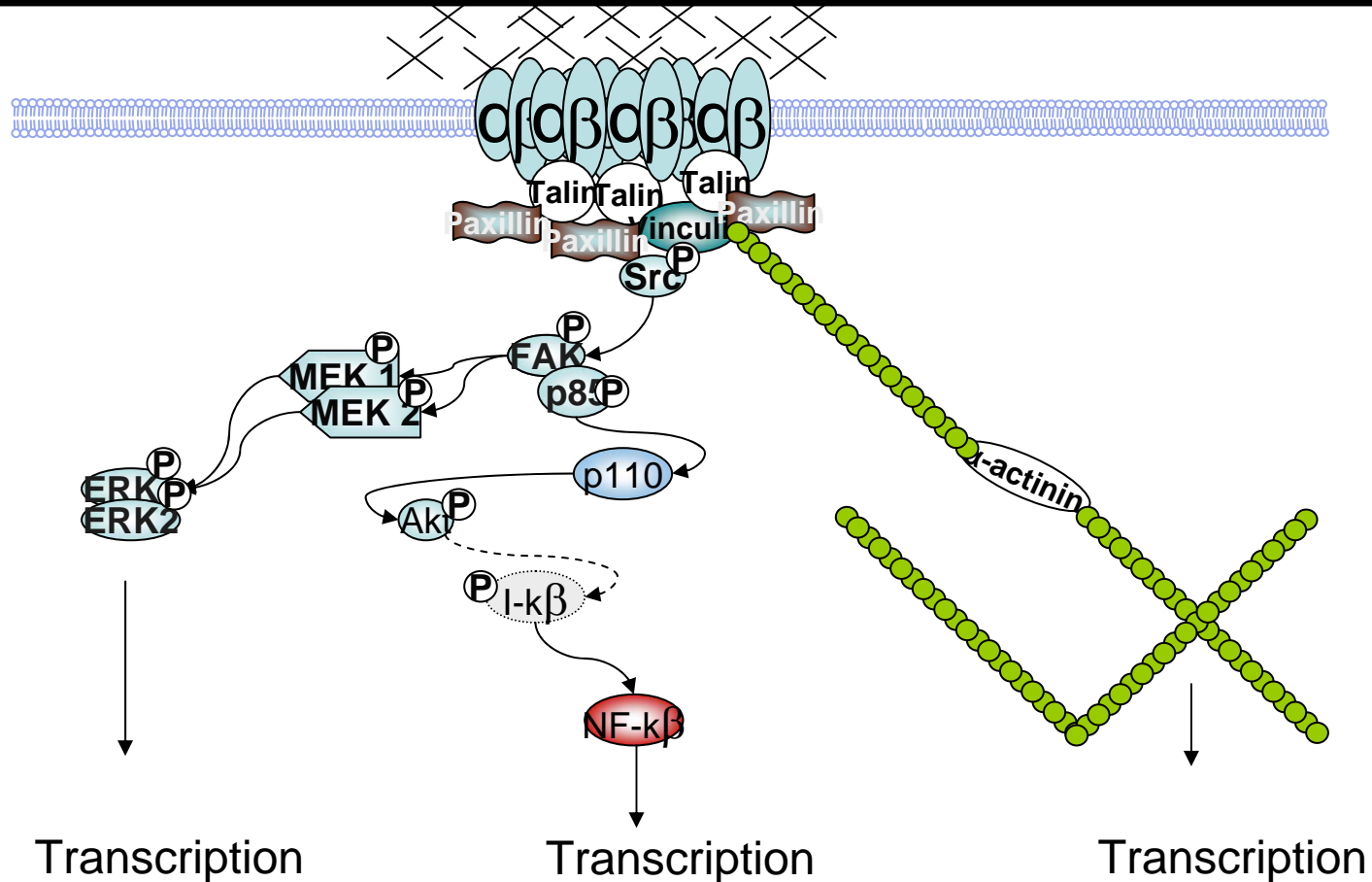
Smith & Nephew R&D

EXOGEN – Mechanism of Action



- LIPUS sends ultrasound waves through the skin and soft tissues, which activates mechanical cell receptors on the cell surface called **integrins**.
- Integrins begin to cluster. This clustering starts an intracellular cascade, stimulating molecules that regulate gene expression to move into the nucleus to perform their function.
- The intracellular cascade results in increased protein expression. .

EXOGEN – Mechanism of Action



BMP-4	VEGF	COX-2	PGE-2	Osteopontin	ALP
BMP-7	IGF-1	Osteocalcin	Osteonectin	MMP-13	

EXOGEN – Mechanism of Action

- Ultrasound generated by EXOGEN causes nano-motion
- Motion detected by integrins
- Multiple pathways
- One of the downstream effects of the intracellular pathways is the production of COX-2
- The effect of COX-2 / PGE2 is to enhance mineralisation

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 17, Number 4, 2002
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Cyclo-Oxygenase 2 Function Is Essential for Bone Fracture Healing

ANN MARE DEMERS¹, MICHAEL BETH MANIGASSO^{1,2}, and MARGARET A. O'CONNOR^{1,3}

ABSTRACT

Despite the molecular and histological similarities between fetal bone development and fracture healing, inflammation is an early phase of fracture healing that does not occur during development. Cyclo-oxygenase 2 (COX-2) is induced at inflammation sites and produces proinflammatory prostaglandins. To determine if COX-2 functions in fracture healing, rats were treated with COX-2-selective nonsteroidal anti-inflammatory drugs (NSAIDs) to stop COX-2-dependent prostaglandin production. Radiographic, histological, and mechanical testing determined that fracture healing failed in rats treated with COX-2-selective NSAIDs (celecoxib and rofecoxib). Normal fracture healing also failed in mice homozygous for a null mutation in the COX-2 gene. This shows that COX-2 activity is necessary for normal fracture healing and confirms that the effects of COX-2-selective NSAIDs on fracture healing is caused by inhibition of COX-2 activity and not from a drug side effect. Histological observations suggest that COX-2 is required for normal endochondral ossification during fracture healing. Because mice lacking *Cox2* form normal skeletons, our observations indicate that fetal bone development and fracture healing are different and that COX-2 function is specifically essential for fracture healing. (J Bone Miner Res 2002;17:963-976)

Key words: cyclo-oxygenase 2, fracture healing, endochondral ossification, nonsteroidal anti-inflammatory drug, prostaglandin

INTRODUCTION

Fracture healing is the culmination of a highly orchestrated series of physiological and cellular pathways to restore the function of broken bone. Osteogenesis during fracture healing occurs by intramembranous and endochondral ossification that resembles fetal osteogenesis¹⁻³. However, the localized tissue hypoxia, the fracture hematoma, and subsequent inflammation at the fracture site, as well as the frank remodeling of the fracture callus at the later stages of healing, are unique physiological and cellular

responses to bone fractures that have no known corresponding counterpart during fetal development of the skeleton.

It has been hypothesized that the early physiological responses to a bone fracture, namely, hypoxia and inflammation, induce gene expression pathways and promote cell proliferation and migration into the fracture site to promote healing.^{4,5} Production or release of specific growth factors, cytokines, and local hormones at the fracture by these physiological processes would cross the appropriate micro-environment to (1) stimulate pericyte osteoblast proliferation and intramembranous ossification at the fracture site, (2) stimulate cell proliferation and migration into the frac-

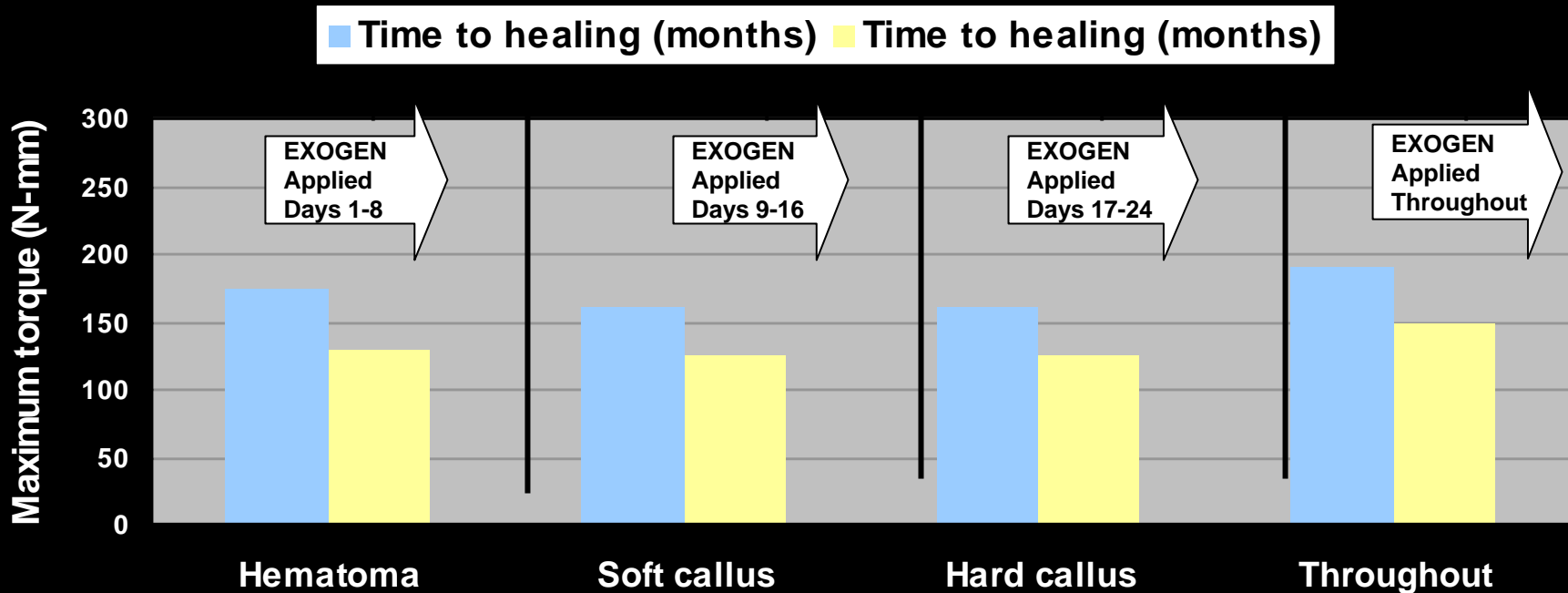
The authors have no conflict of interest.

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³Department of Microbiology and Molecular Genetics, UMDOJ-New Jersey Medical School, Newark, New Jersey, USA.

EXOGEN – Mechanism of Action



- Has a biological impact and accelerates every phase of fracture healing

EXOGEN Summary

- Compelling evidence for acceleration of certain fresh fractures
- “Lower quality” nonunion studies – BUT consistency of effect across multiple studies increases confidence
- Mechanism of action elucidated – no longer a black box technology
- Biologic impact across all phases of fracture healing
- Important societal benefits and cost savings

Thank You

Agency Medical Director Comments

Bone Growth Stimulation
WA State Agency Data



**Washington State
Health Care Authority**

Background

- 7.9 million bone fractures in the US
- 5-10% healing is delayed or impaired
- Bone union is a concern both in fractures, fusions, and risk for arthrodesis.



Bone Growth Stimulators

- Electrical

 - Non-invasive/external placement

 - Semi-invasive (no longer used)

 - Invasive/implantable

- Ultrasound



Scientific Evidence

- Conflicting, moderate to low quality
- Systematic reviews reveals variation across studies
- No recent studies for effect of different treatment parameters
- No elucidated specific factors for use in fresh fractures
- No clearly identified factors for treatment success



Scientific Evidence

- The validity of patient compliance is not known
- No controlled studies compared the use of BGS with and without concomitant treatment.
- There is no high quality studies for direct comparison between types of BGS
- No blinded assessment of X-rays following invasive procedure



SAFETY and EFFECTIVENESS

- Ultrasound and non-invasive BGS no serious concerns
- Increased complications with invasive devices in high risk patients
- No studies looking at patients by age groups
- No clearly identified factors for treatment success



Coverage

- Variation in coverage by commercial plans
- L& I criteria similar to CMS
- DSHS and UMP-Hayes
- CMS-National coverage decision for electrical stimulation for non-union of long bones, failed spinal fusion, and adjunct to spinal fusion; and ultrasound for non-union of bones

Procedure Code by Year

PROC CODE (ICD-9, CPT, HCPCS)	2005	2006	2007	2008	Total
78.91 (Invasive electrical,	0	0	0	1	1
78.94 (Invasive electrical,	1	0	0	0	1
78.95 (Invasive electrical,	0	1	0	0	1
78.97 (Invasive electrical,	1	0	0	1	2
78.98 (Invasive electrical, tarsals, metatarsals)	1	0	0	2	3
78.99 (Invasive electrical, spine, pelvis, phalanges)	4	6	4	1	15
20974 (Noninvasive electrical)	14	11	2	7	34
20975 (Invasive electrical)	12	7	5	10	34
20979 (Noninvasive ultrasound)	3	3	3	6	15
E0747 (Noninvasive electrical, other than spine)	130	157	134	138	559
E0748 (Noninvasive electrical, spine)	50	28	80	86	244
E0749 (Invasive, electrical)	0	0	0	0	0
E0760 (Noninvasive ultrasound)	39	45	47	60	191
Total	255	258	275	312	1100

ICD-9, CPT, HCPCS codes are unduplicated counts. HCPCS codes not available for cases listed by ICD-9 or CPT code. Counts for E0749 not available due to bundled billing.



Diagnoses by Procedure Code

UMP, Medicaid, L&I 2005-2008	HCPCS CODE			
	E0747	E0748	E0760	Total
Principal ICD-9 Diagnosis				
Nonunion of fracture	170	1	5	176
Arthrodesis status	27	87	0	114
Fracture metatarsal-closed	26	0	44	70
Back disorder NOS	4	17	0	21
Fracture ankle NOS-closed	0	0	13	13
Total	227	105	62	394



Distribution of Procedures by Bone Type

UMP, Medicaid, L&I | 2005-2008

HCPCS CODE	Bone Type			
	Long	Spine	Other*	Total
E0747 (Noninvasive electrical, other than spine)	109	7	443	559
E0748 (Noninvasive electrical, spine)	0	203	61	264
E0760 (Noninvasive ultrasound)	72	0	121	193
Total	181	210	625	1016

* Other bones typically include bones of the hand and foot.



Average* Payments by Procedure

UMP, Medicaid, L&I | 2005-2008

HCPCS CODE	Average Payments
E0747 (Noninvasive electrical, other than spine)	\$3,688
E0748 (Noninvasive electrical, spine)	\$3,537
E0760 (Noninvasive ultrasound)	\$2,820

* Weighted average



Total Payments by Procedure by Year

UMP, Medicaid, L&I | 2005-2008

HCPCS CODE	2005	2006	2007	2008	Total
E0747	\$503,083	\$573,974	\$488,099	\$489,267	\$2,054,424
E0748	\$186,835	\$89,177	\$265,033	\$311,419	\$852,464
E0760	\$101,781	\$124,291	\$130,185	\$179,616	\$535,873
Total	\$791,700	\$787,442	\$883,317	\$980,302	\$3,442,761





Economic Studies

Evidence does not demonstrate consistent outcomes across populations; therefore, economic studies are not appropriate until large randomized control and observational studies are done.

Recommendations

- Larger randomized trials and observational studies are needed to:
 - * confirm positive benefits
 - * identify any rare adverse events
 - * demonstrate effectiveness/safety
 - * identify patient selection criteria
- Non-coverage or very limited coverage
Ex. for patients at high risk for psuedo-arthrosis following fusion.



HTCC Coverage and Reimbursement Determination Analytic Tool

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

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

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

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

Principle One: Determinations are Evidence based

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

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

Principle Two: Determinations result in health benefit

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

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

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

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

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Using Evidence as the basis for a Coverage Decision

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

1. **Availability of Evidence:**

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

2. **Sufficiency of the Evidence:**

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

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

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

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

3. **Factors for Consideration - Importance**

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

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

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

Medicare Coverage and Guidelines

Organization	Date	Outcome	Evidence Cited?	Grade / Rating
<p>CMS Coverage Database 150.2</p> <p>Technology Assessment 2005</p>	<p>2005</p>	<p>There is a National Coverage decision. Electrical noninvasive and invasive stimulator device is covered only for the following indications:</p> <ul style="list-style-type: none"> Nonunion of long bone fractures (3 or more months ceased healing, 2 radiographs min. 90 days apart); Failed fusion, where a minimum of 9 months has elapsed since the last surgery; or adjunct to fusion for patients with a previously failed fusion and high risk of psuedarthrosis Congenital pseudarthroses (noninvasive only) <p>Ultrasonic stimulator</p> <ul style="list-style-type: none"> Nonunion confirmed by 2 radiographs min. 90 days apart and physician statement of no clinical evidence of fracture healing <p>Non covered indications –</p> <ul style="list-style-type: none"> Nonunion of skull, vertebrae or tumor related Ultrasonic stimulator – fresh, delayed fractures and concurrent use with other noninvasive stimulator <p>A technology assessment was prepared for CMS by AHRQ in 2005. Overall conclusion “Thus, the overall quality of the evidence for each type of intervention is for the most part low, and few of the studies can actually be used to distinguish the effect of the device or orthobiologics agent from the additional treatments these patients received..”</p>	<p>Yes</p>	<p>Low</p>
<p>Guidelines – WA HTA p. 79</p>	<p>2005</p>	<p>American Association of Neurological Surgeons/Congress of Neurological Surgeons 2005</p> <p>Includes treatment standards and treatment guidelines related to lumbar surgery and BGS.</p> <p><i>Treatment Standard:</i> Insufficient evidence to recommend a treatment standard.</p> <p><i>Treatment Guidelines.</i> Either DCS or CCS is recommended as an adjunct to spinal fusion to increase fusion rates in patients who are at high risk for arthrodesis failure following lumbar PLF. Pulsed electromagnetic field stimulation is recommended as an adjunct to increase fusion rates in similar patients treated with lumbar interbody fusion procedures.</p>	<p>Yes</p>	<p>There is no consistent medical evidence to support or refute use of these devices for improving patient outcomes</p>

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

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

	Electrical Non-Invasive	Electrical Invasive	Ultrasound
Safety			
Mortality			
Morbidity			
Efficacy-Effectiveness			
Healing Promotion			
Pain Reduction			
Improve Function			
Stimulation parameters, duration			
Fracture type- fresh, delayed, non-union, surgical,			
Other			
Special Population/ Considerations			
Long Bone			
Spinal Fusion			
Other Bones			
Comorbidities or risk factors			
Other			
Cost			

Safety Outcomes	Safety Evidence
Mortality - Overall Mortality	
Morbidity -	
Efficacy/Effectiveness Outcomes	Efficacy/Effectiveness Evidence
Cost Outcomes	Cost Evidence
Other Factors	Evidence
Special Populations	

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?