Orthobiologics for Spine Conditions

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Disclosures

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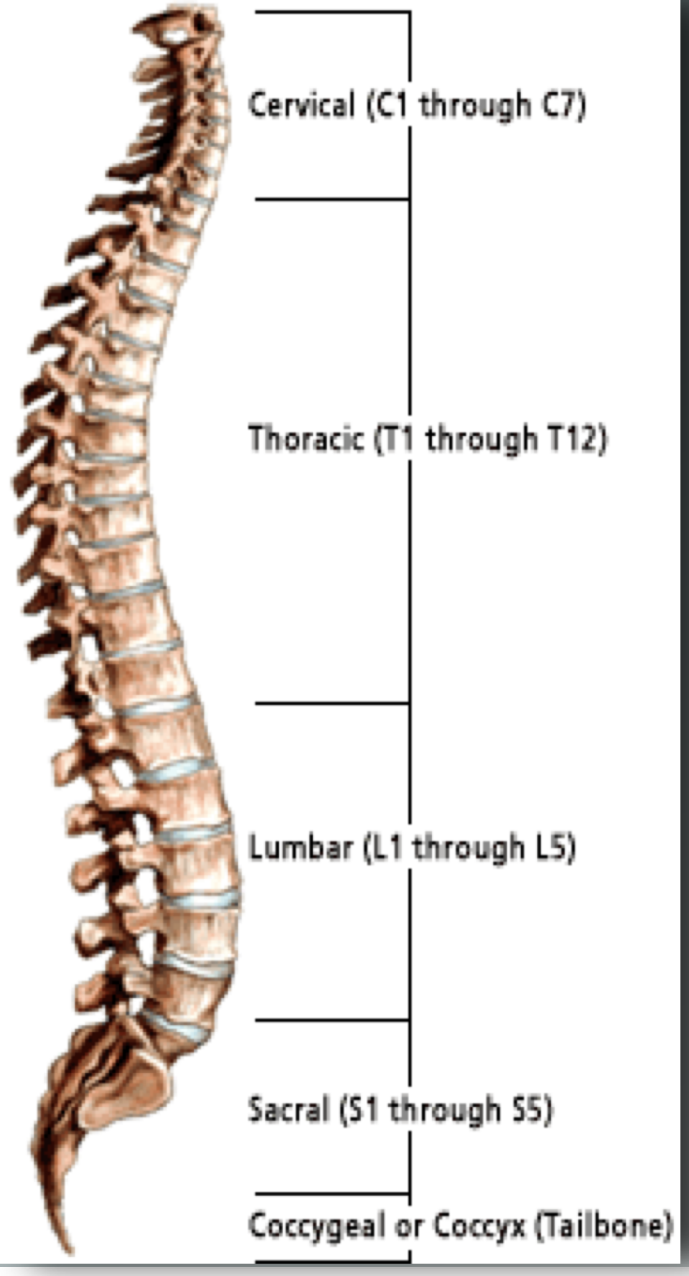
Learning Objectives

- Spine Anatomy
- Pain Generators of the Spine
- Non-Operative Pain Management
- Why Injection Therapy?
- Orthobiologic Applications:

  - Bone Marrow Concentrate



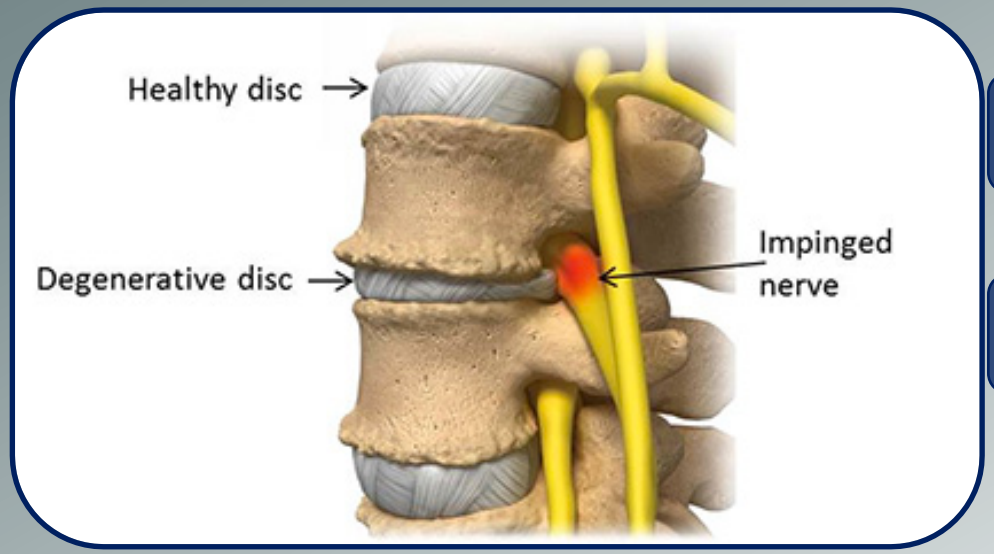
Spine Anatomy

- Spine function – provides flexibility, protection of spinal cord
- Discs – shock absorbers, rotation
- Facet “Joints” – stabilizers, “doorstops”

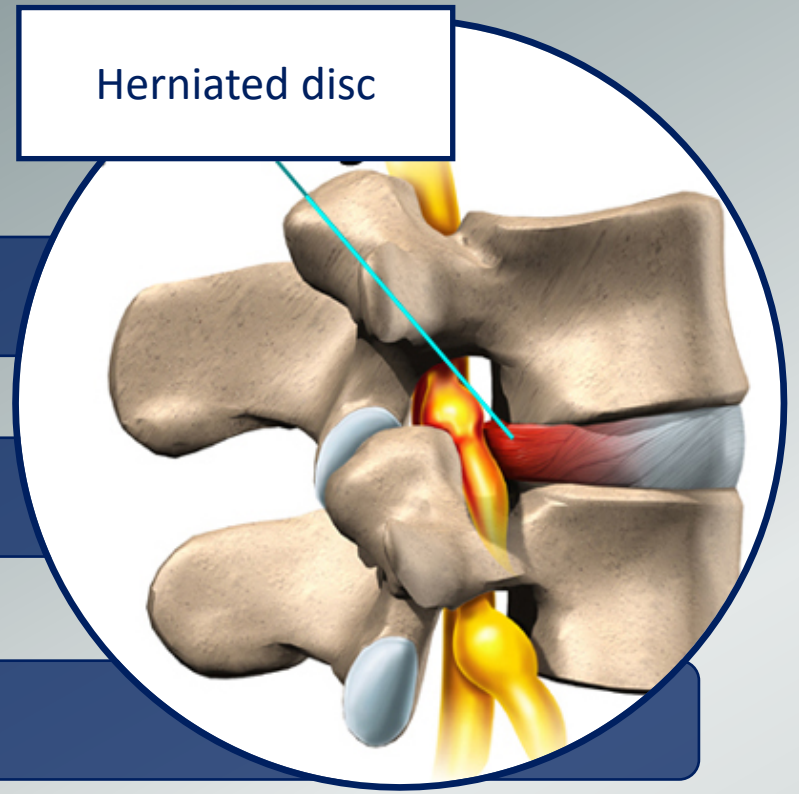
Pain Generators

Facet mediated pain

Disc Pain



Herniated disc



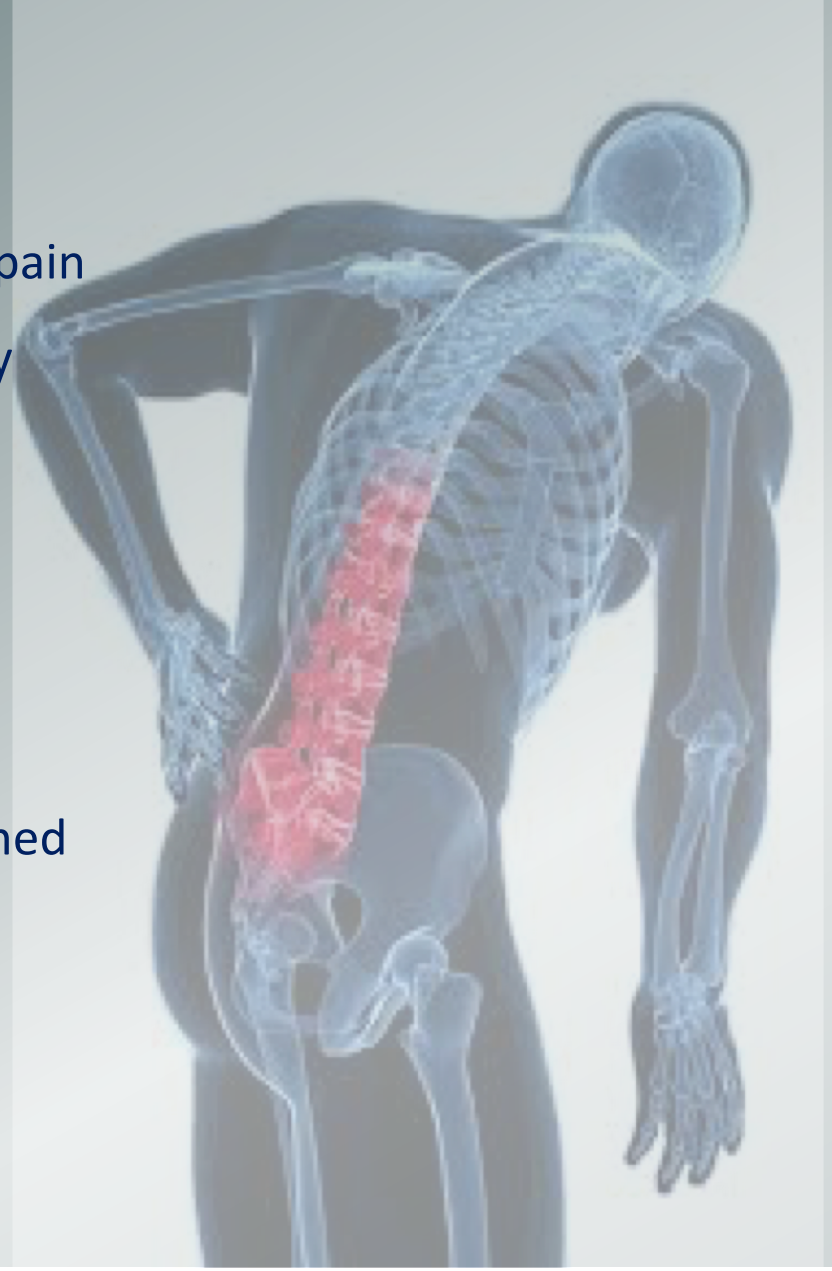
Myofascial pain

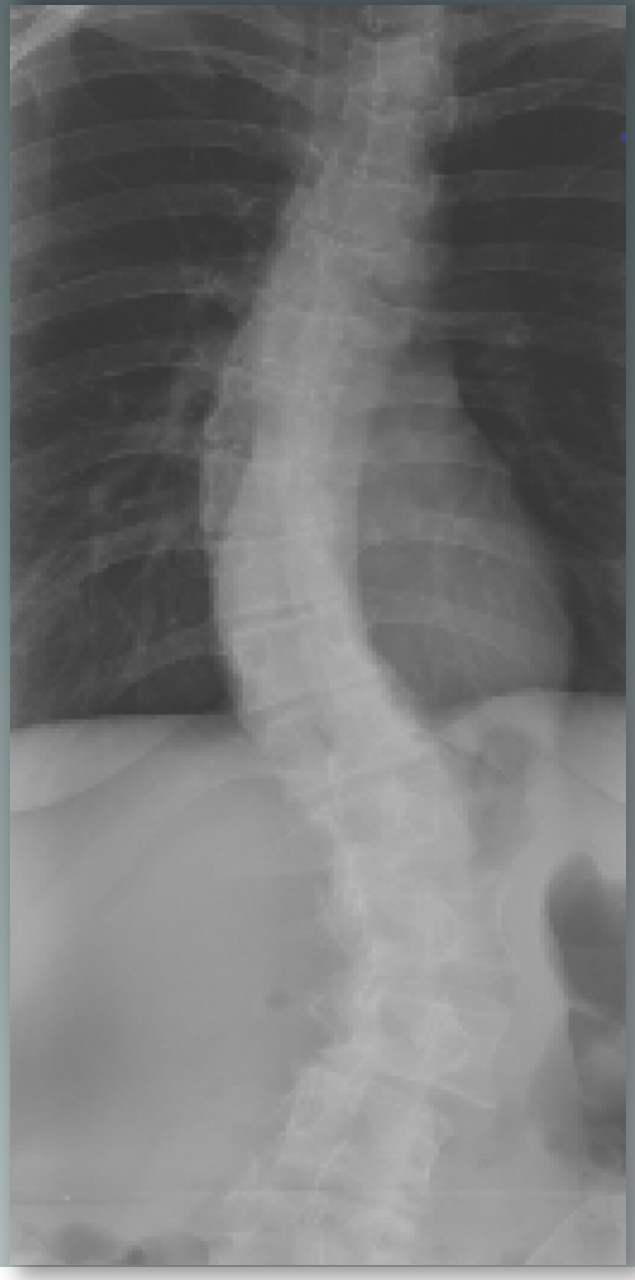
Other

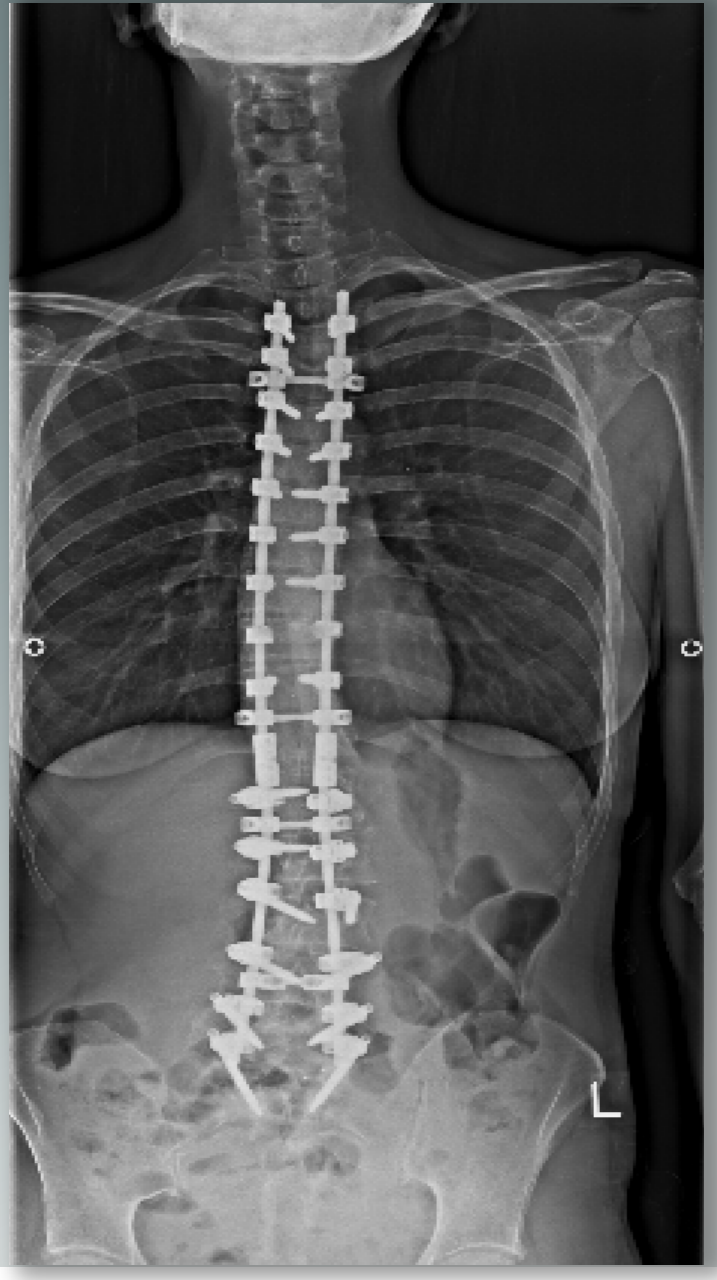
The Impact of Back Pain

Navani et al. 2017

- 8 out of 10 Americans will experience back pain
- Worldwide – Back pain #1 cause of disability
- Primary reason for missed work in the US
- **>2 million lumbar epidural injections** are performed on Medicare patients annually
- $9B spent globally on spine surgery in 2017
- 1.62M instrumental procedures are performed annually



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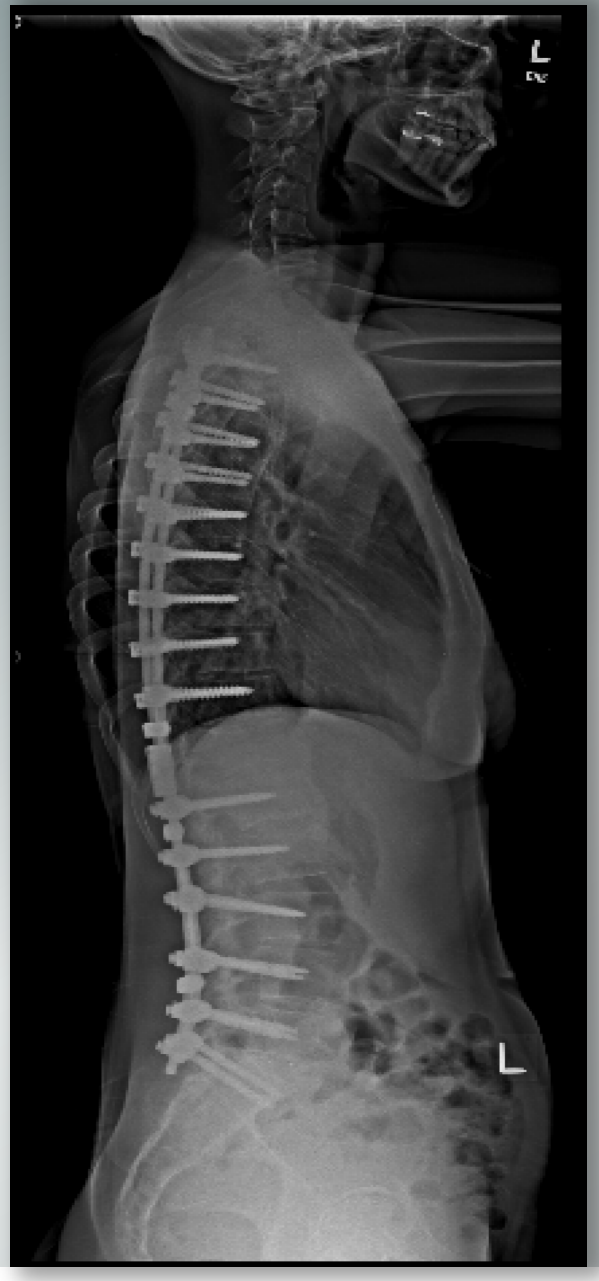
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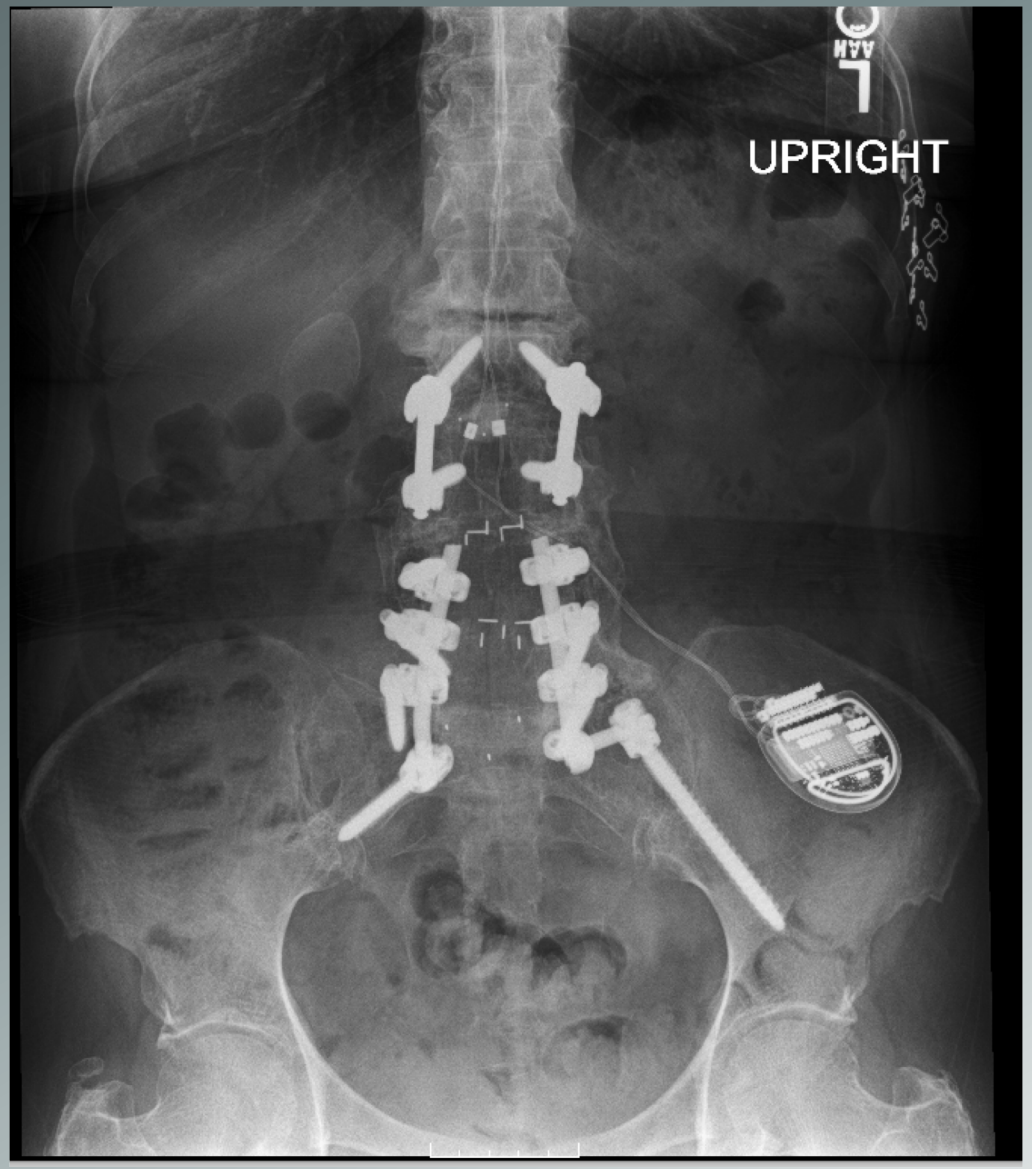
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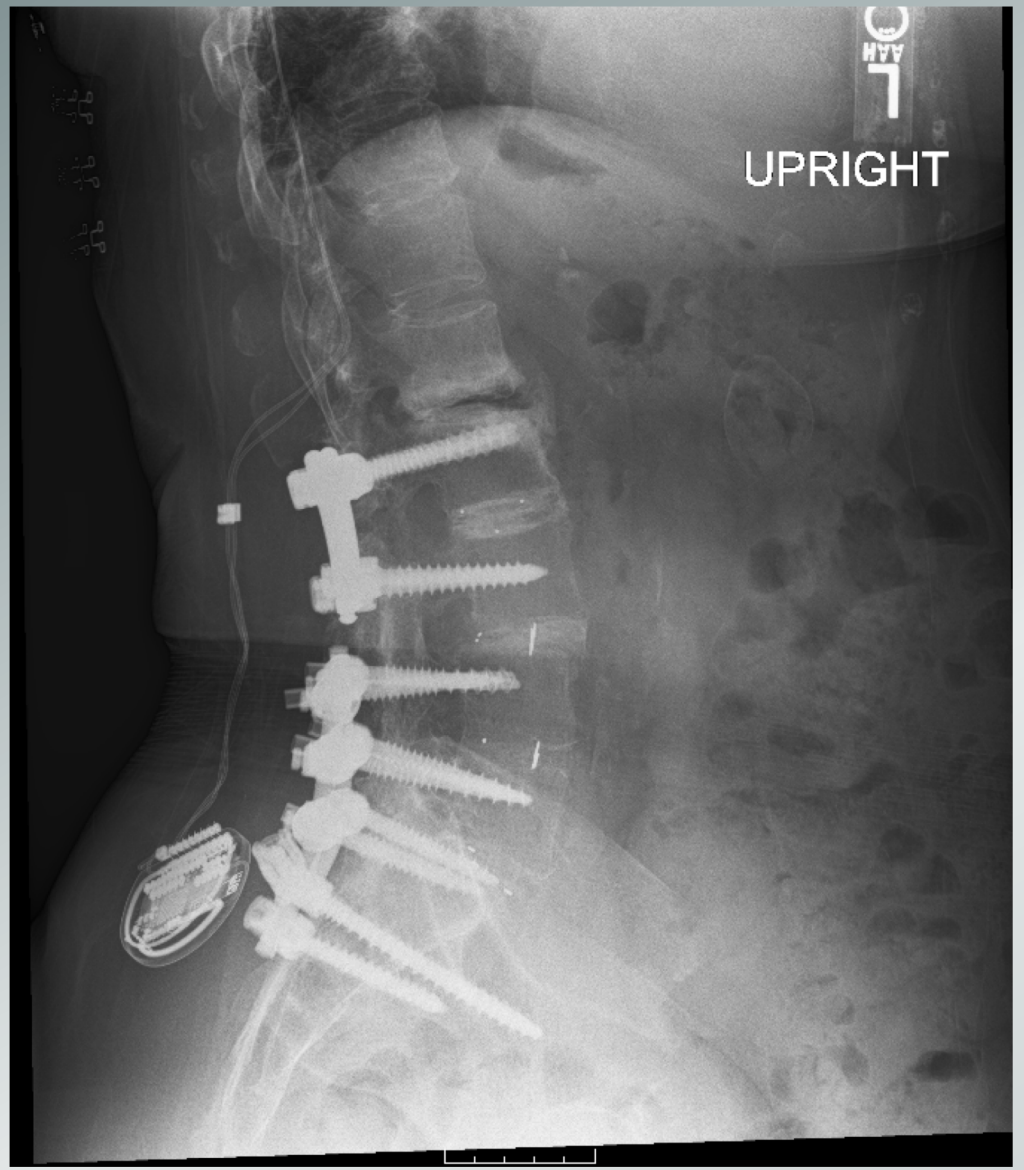
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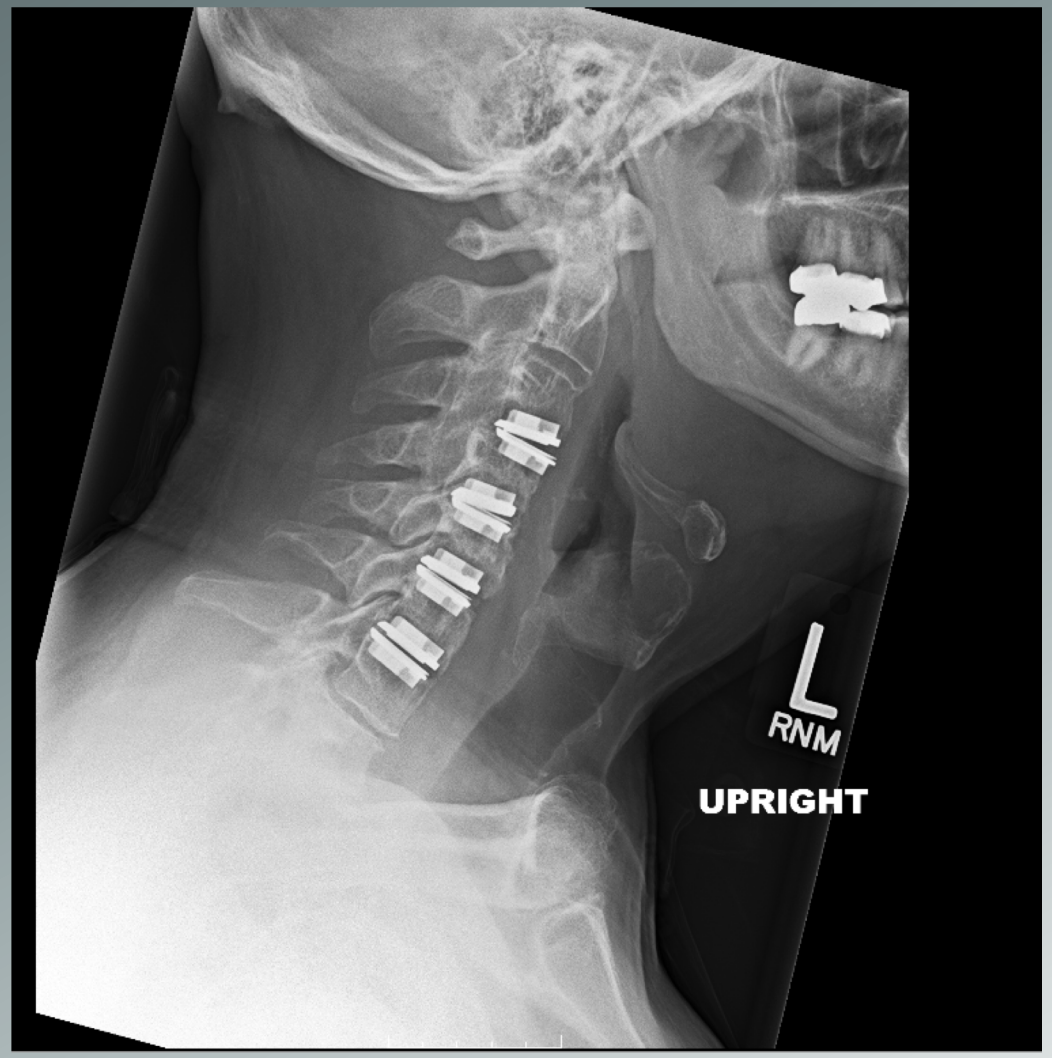
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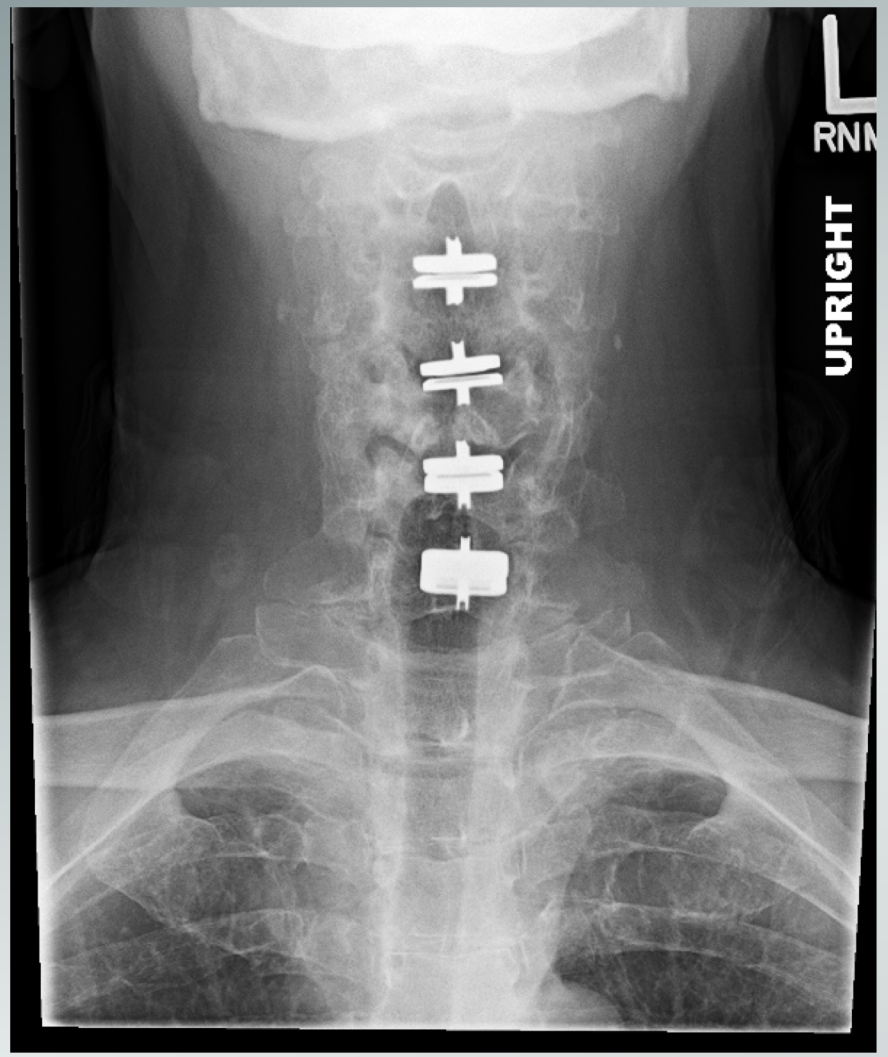
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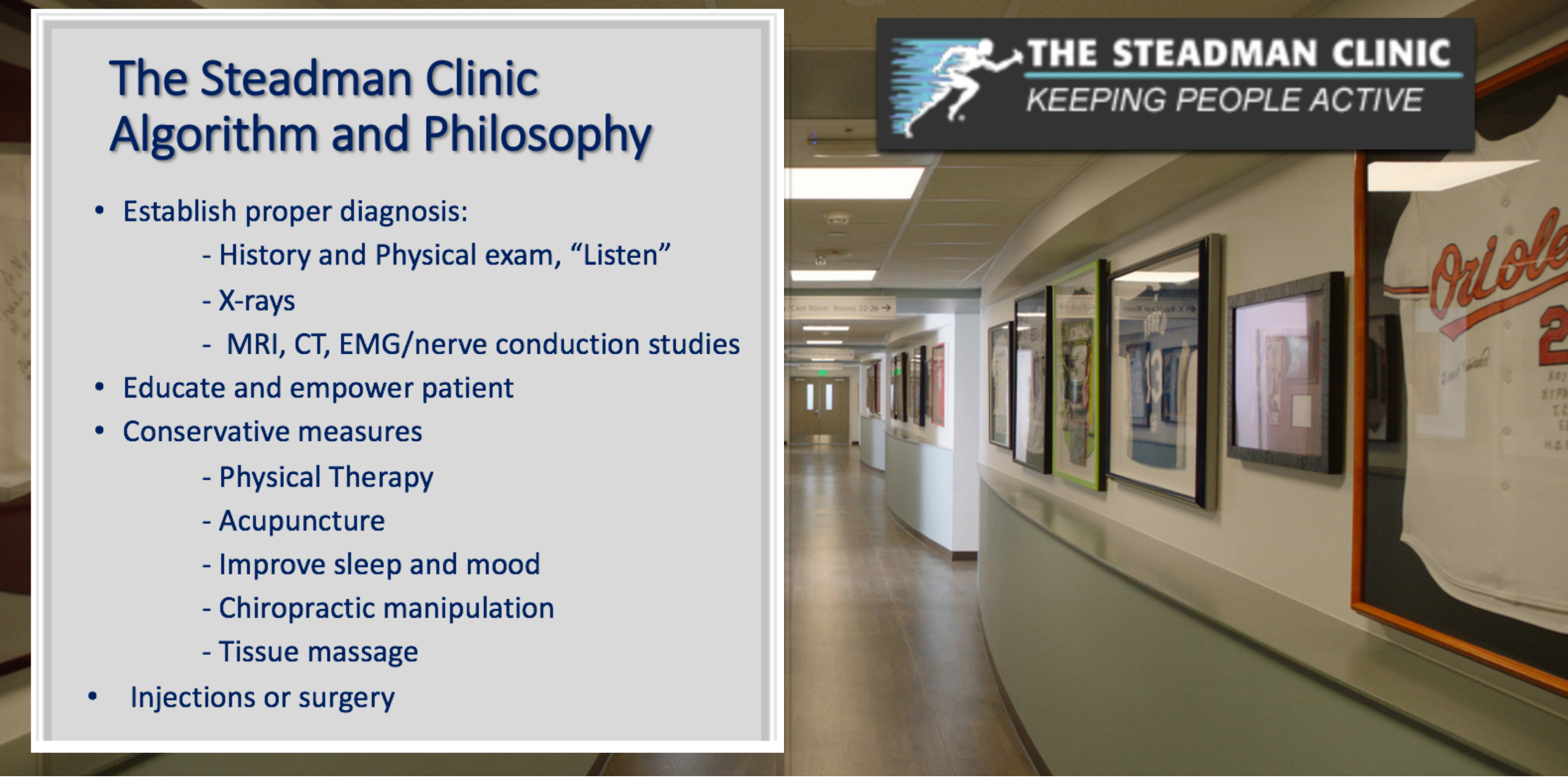
UPRIGHT

The Steadman Clinic Algorithm and Philosophy

- Establish proper diagnosis:
  - History and Physical exam, “Listen”
  - X-rays
  - MRI, CT, EMG/nerve conduction studies
- Educate and empower patient
- Conservative measures
  - Physical Therapy
  - Acupuncture
  - Improve sleep and mood
  - Chiropractic manipulation
  - Tissue massage
- Injections or surgery



Non-Operative Pain Management Strategies

Steroid Injection Treatments:

Diagnostic Injections:
- Identify source of problem

Therapeutic Injections:
- Decrease or resolve pain
- Improve overall function

Steroid Injection Treatment

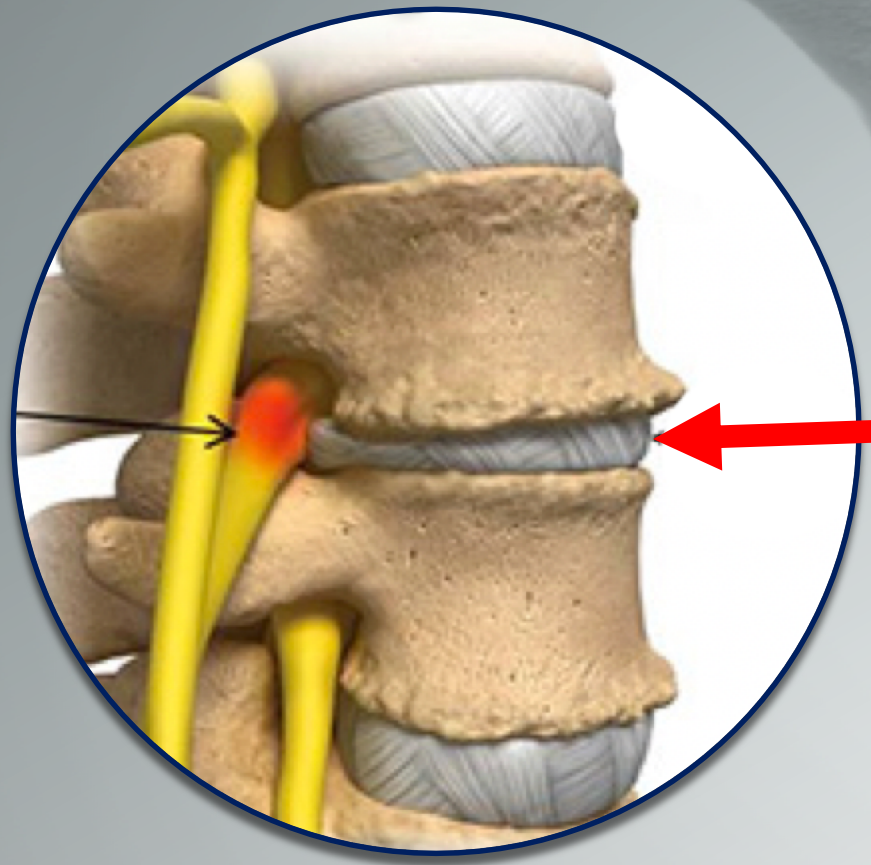
PROs

- Immediate relief
- Delays or prevents operative intervention
- Potent anti-inflammatory

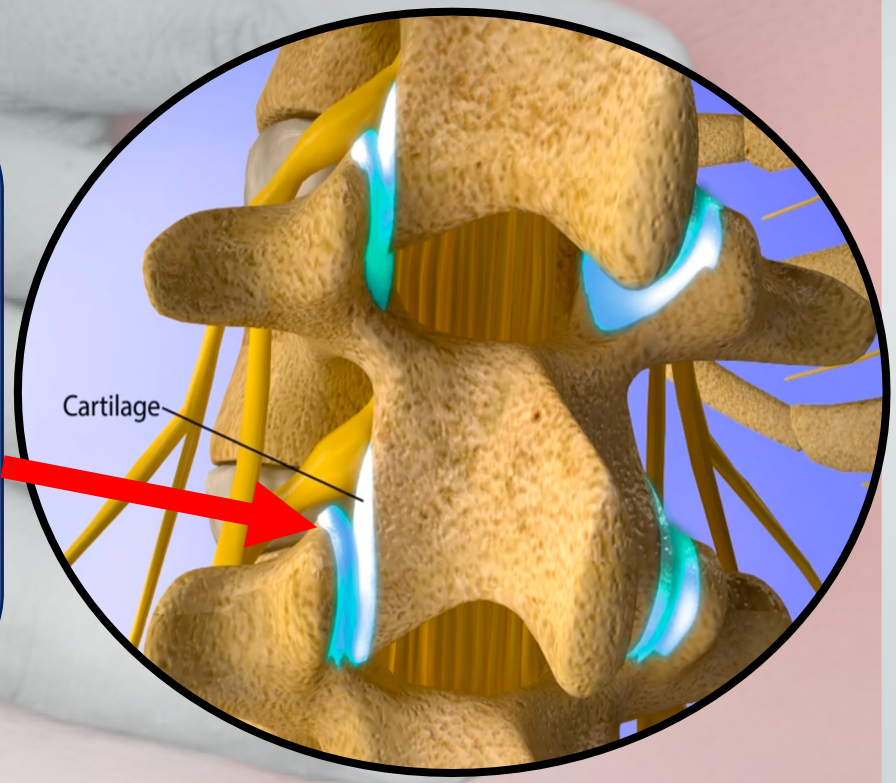
CONs

- Non-regenerative
- Tendon rupture
- Short-term solution
- Adrenal suppression
- Possible infection
- Pericapsular joint calcification
- Skin atrophy/depigmentation

Non-Operative Pain Management Strategies



Can we treat DDD and facet joint arthritis with Bone Marrow Concentrate?



What is Bone Marrow Concentrate?

FDA Cells, Tissues, Cellular/tissue-based Products

High Risk 351 Products

- Preclinical animal trials or
- Strong regulatory oversight

NOT APPROVED

Stem Cells

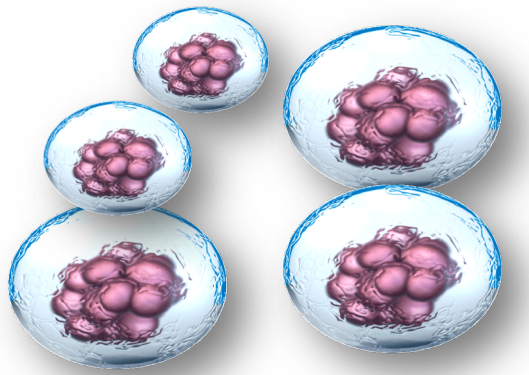
Low Risk 361 Products

- **No** Preclinical animal trials or
- Less St
- Less M
- **Little regulatory oversight**

APPROVED

Bone Marrow Concentrate

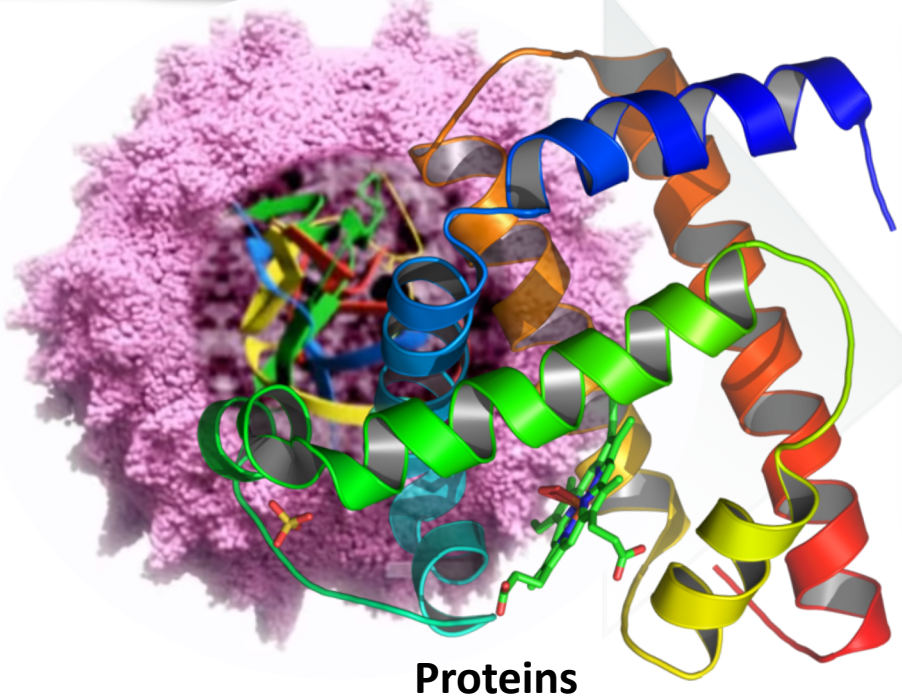
What is Bone Marrow Concentrate?



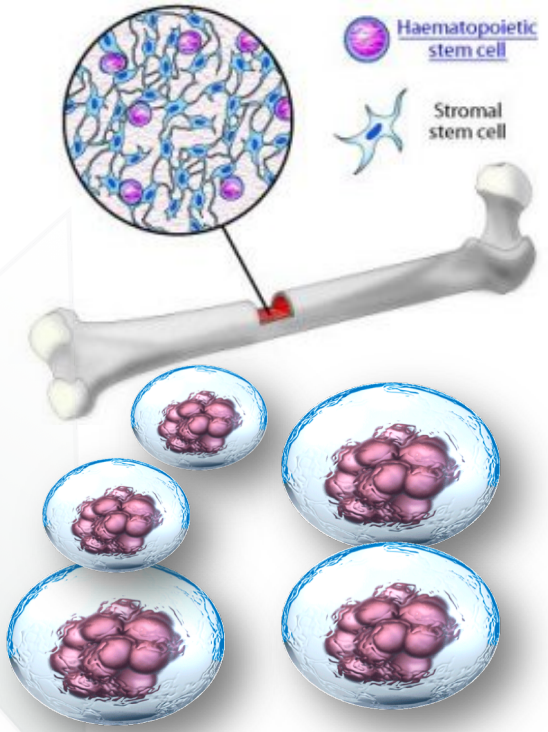
Millions of “isolated” stem cells

What is Bone Marrow Concentrate?

What is Bone Marrow Concentrate?

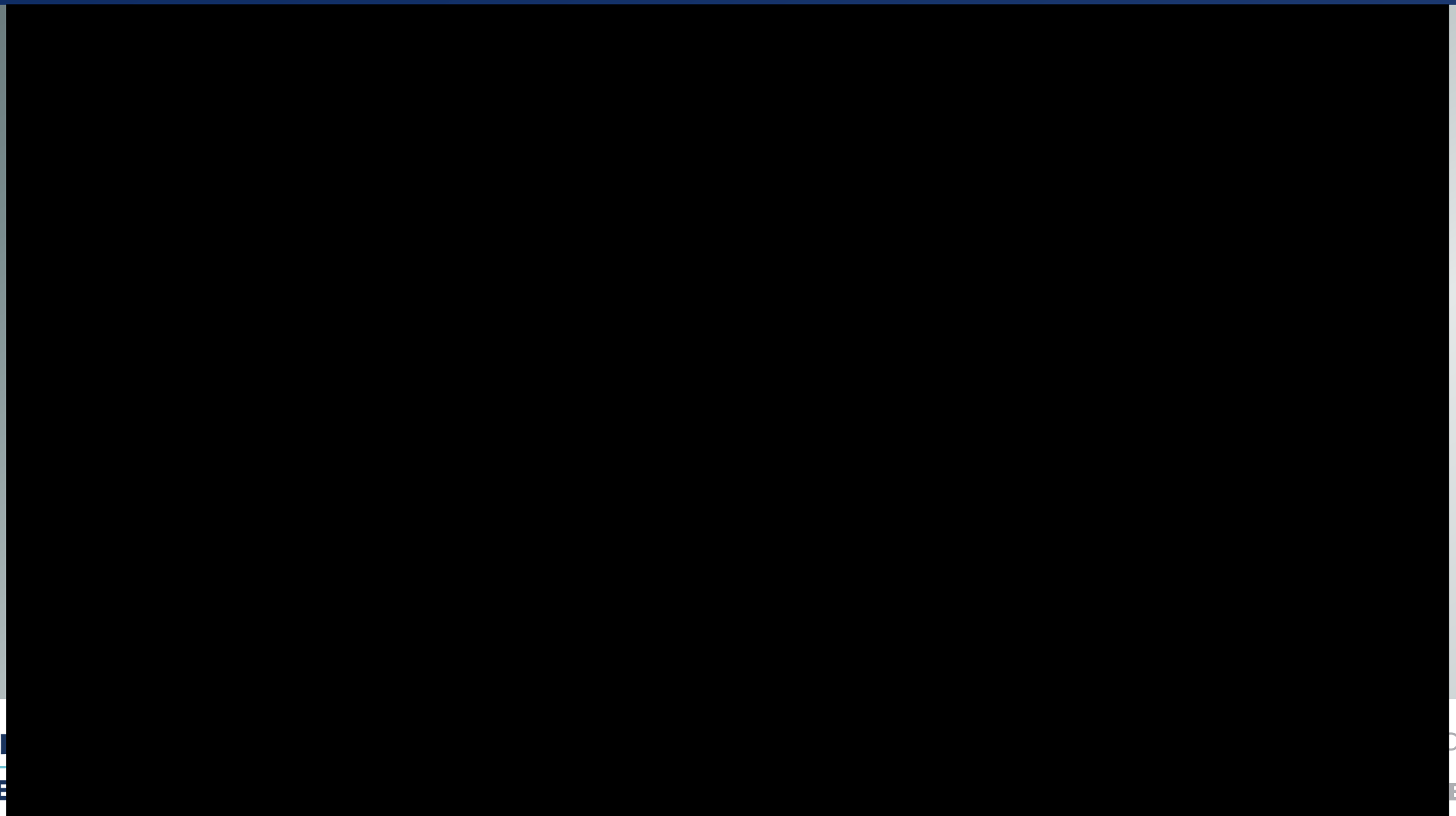


Proteins
Bioactive Factors



Progenitor Stem Cells

Bone Marrow Procedure



What We Know About Bone Marrow Application for Degenerative Disc Disease

STEM CELLS

TRANSLATIONAL AND CLINICAL RESEARCH

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Percutaneous Injection of Autologous Bone Marrow Concentrate Cells Significantly Reduces Lumbar Discogenic Pain through 12 Months

Kenneth A. Pettine, M.D.,[1] Matthew B. Murphy, Ph.D.,[2,3] Richard K. Suzuki, Ph.D.,[3] Theodore T. Sand, Ph.D.[3]

Key Words. Autologous cell therapy • mesenchymal stem cells • bone marrow concentrate • intervertebral disc injection

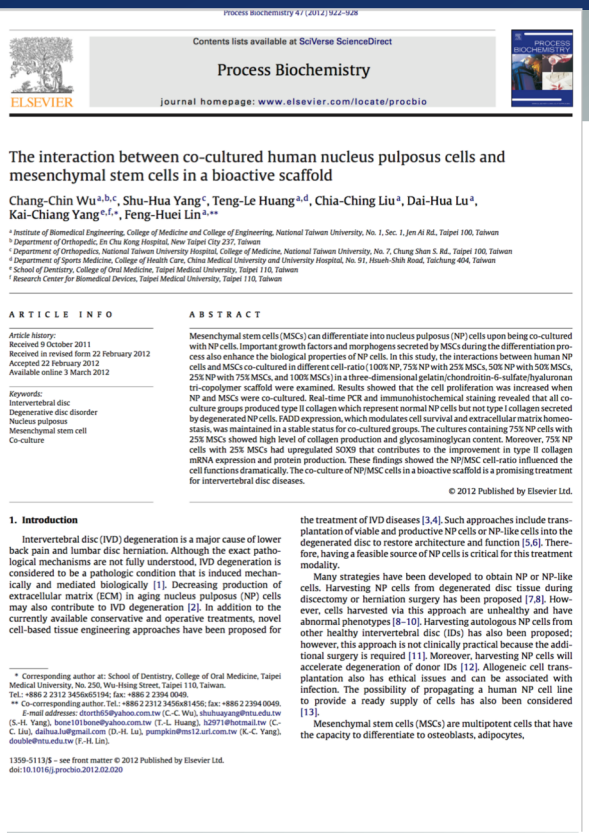
ABSTRACT

Degenerative disc disease (DDD) induces chronic back pain with limited non-surgical options. In this open label pilot study, twenty-six patients (median age 40 years; range 18-61) received autologous bone marrow concentrate (BMC) disc injections (13 one level, 13 two levels). Pre-treatment Oswestry Disability Index (ODI) and Visual Analogue Scale (VAS) were performed to establish baseline pain scores (average 56.5 and 79.3 respectively), while MRI were independently scored according to the modified Pfirrmann scale. Approximately 1 mL of BMC was analyzed for total nucleated cell (TNC) content, colony forming unit-fibroblast (CFU-F) frequency, differentiation potential, and phenotype characterization. The average ODI and VAS scores were reduced to 22.8 and 29.2 at 3 months, 24.4 and 26.3 at 6 months, and 25.0 and 33.2 at 12 months, respectively (ps≤0.0001). Eight of 20 patients improved by one modified Pfirrmann grade at one year. The average BMC contained 121x10^6 TNC/mL with 2,713 CFU-F/mL (synonymous with mesenchymal stem cells). Although all subjects presented a substantial reduction in pain, patients receiving greater than 2,000 CFU-F/mL experienced a significantly faster and greater reduction in ODI and VAS. Subjects older than 40 years who received fewer than 2,000 CFU-F/mL experienced an average pain reduction of 33.7% (ODI) and 29.1% (VAS) at 12 months, while all other patients' average reduction was 69.5% (ODI, p=0.03) and 70.6% (VAS, p=0.01). This study provides evidence of safety and feasibility in the non-surgical treatment of DDD with autologous BMC and indicates an effect of mesenchymal cell concentration on discogenic pain reduction. STEM CELLS *2014; 00:000–000*

INTRODUCTION

Degenerative disc disease is a progressive deterioration of intervertebral discs causing a loss of disc height and pain. Back pain affects millions of Americans and results in billions of dollars in lost income and medical expenses annually. In fact, degenerative changes in lumbar discs are so ubiquitous that they are considered "a normal aging process," as documented in several magnetic resonance imaging (MRI) scan studies [1–3]. However, the exact cause of disc degeneration is complicated. Various animal studies have been contradictory in directly correlating biomechanical stress and disc degeneration [4–11]. Likewise, published clinical studies have failed to link disc degeneration directly to mechanical factors such as labor-intensive [12,13]. As a further complication, the perception of pain in humans is complex, related to psychosocial factors, environmental factors and one's perception of life's satisfaction [12–19].

Disc degeneration on a cellular level also is complicated. Nutrients must travel through the capillary network in the vertebral body, then diffuse through the endplate into the extracellular matrix of the disc to reach the



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The interaction between co-cultured human nucleus pulposus cells and mesenchymal stem cells in a bioactive scaffold

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Co-culture

ABSTRACT

Mesenchymal stem cells (MSCs) can differentiate into nucleus pulposus (NP) cells upon being co-cultured with NP cells. Important growth factors and morphogens secreted by MSCs during the differentiation process also enhance the biological properties of NP cells. In this study, the interactions between human NP cells and MSCs co-cultured in different cell-ratio (100% NP, 75% NP with 25% MSCs, 50% NP with 50% MSCs, 25% NP with 75% MSCs, and 100% MSCs) in a three-dimensional gelatin/chondroitin-6-sulfate/hyaluronan tri-copolymer scaffold were examined. Results showed that the cell proliferation was increased when NP and MSCs were co-cultured. Real-time PCR and immunohistochemical staining revealed that all co-culture groups produced type II collagen which represent normal NP cells but not type I collagen secreted by degenerated NP cells. FADD expression, which modulates cell survival and extracellular matrix homeostasis, was maintained in a stable status for co-cultured groups. The cultures containing 75% NP cells with 25% MSCs showed high level of collagen production and glycosaminoglycan content. Moreover, 75% NP cells with 25% MSCs had upregulated SOX9 that contributes to the improvement in type II collagen mRNA expression and protein production. These findings showed the NP/MSC cell-ratio influenced the cell functions dramatically. The co-culture of NP/MSC cells in a bioactive scaffold is a promising treatment for intervertebral disc diseases.

1. Introduction

Intervertebral disc (IVD) degeneration is a major cause of lower back pain and lumbar disc herniation. Although the exact pathological mechanisms are not fully understood, IVD degeneration is considered to be a pathologic condition that is induced mechanically and mediated biologically [1]. Decreasing production of extracellular matrix (ECM) in aging nucleus pulposus (NP) cells may also contribute to IVD degeneration [2]. In addition to the currently available conservative and operative treatments, novel cell-based tissue engineering approaches have been proposed for the treatment of IVD diseases [3,4]. Such approaches include transplantation of viable and productive NP cells or NP-like cells into the degenerated disc to restore architecture and function [5,6]. Therefore, having a feasible source of NP cells is critical for this treatment modality.

Many strategies have been developed to obtain NP or NP-like cells. Harvesting NP cells from degenerated disc tissue during discectomy or herniation surgery has been proposed [7,8]. However, cells harvested via this approach are unhealthy and have abnormal phenotypes [8–10]. Harvesting autologous NP cells from other healthy intervertebral disc (IDs) has also been proposed; however, this approach is not clinically practical because the additional surgery is required [11]. Moreover, harvesting NP cells will accelerate degeneration of donor IDs [12]. Allogeneic cell transplantation also has ethical issues and can be associated with infection. The possibility of propagating a human NP cell line to provide a ready supply of cells has also been considered [13].

Mesenchymal stem cells (MSCs) are multipotent cells that have the capacity to differentiate to osteoblasts, adipocytes,

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REVIEW

Regeneration of intervertebral disc by mesenchymal stem cells: potentials, limitations, and future direction

Victor Y. L. Leung · Danny Chan · Kenneth M. C. Cheung

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Abstract Over the past few years, substantial progress has been made in the field of stem cell regeneration of the intervertebral disc. Autogenic mesenchymal stem cells in animal models can arrest intervertebral disc degeneration or even partially regenerate it and the effect is suggested to be dependent on the severity of degeneration. Mesenchymal stem cells (MSCs) are able to escape alloantigen recognition which is an advantage for allogenic transplantation. A number of injectable scaffolds have been described and various methods to pre-modulate MSCs' activity have been tested. In future, work will need to address the use of mesenchymal stem cells in large animal models and the fate of the implanted mesenchymal stem cells, particularly in the long term, in animals. This review examines the state-of-the-art in the field of stem cell regeneration of the intervertebral disc, and critically discusses, with scientific support, the issues involved, before stem cells could be used in human subjects.

Keywords Mesenchymal stem cells · Intervertebral disc degeneration · Intervertebral disc regeneration · Tissue engineering

Stem cells in orthopaedics

Stem cells are defined as unspecialized cells capable of long-term self-renewal and differentiation into specialized cells. Properties and functions of stem cells have been extensively studied in the development of organisms [33], cancer [56], wound healing [62, 69], and regenerative medicine. In the latter, it has been investigated for tackling complex pathogenic conditions such as neurodegenerative diseases [38], hematopoietic impairment [59], and musculoskeletal degeneration [79, 81]. In the development of organism, the single totipotent cell after fertilization divides and specializes into pluripotent cells, such as embryonic stem cells that are necessary for fetal development. The pluripotent cells then further specialize into multipotent cells that commit into lineages with tissue-specific functions. Cells have been successfully identified in or isolated from embryonic [70], fetal [34, 73], or adult tissues [45] and demonstrated to have stem cell-like properties in vitro and in vivo. The maintenance, survival and activity of these stem cells is suggested to be dependent on the special micro-environmental niche [45], such that uncommitted pluripotent stem cells can be induced to differentiate to form a particular cell type by the nature of the environment. Additionally, the pluripotency of stem cells depends on the source, the method of isolation, and conditions of ex-vivo cell processing.

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Bone Marrow for Degenerative Disc: Results

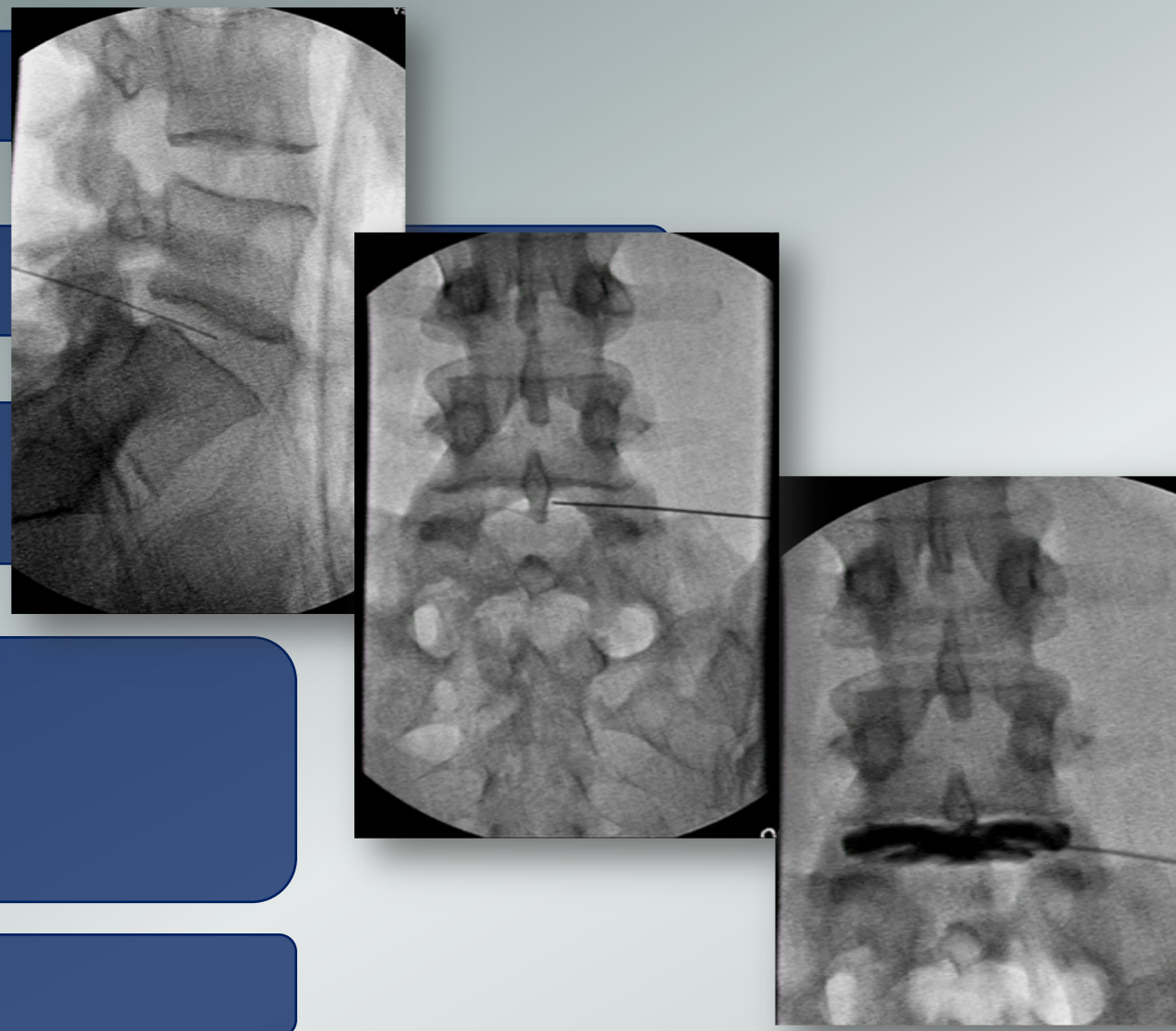
Age range: 16-61 years (median 43)

8 patients treated

Baseline Pain (VAS) scores - average 7.5

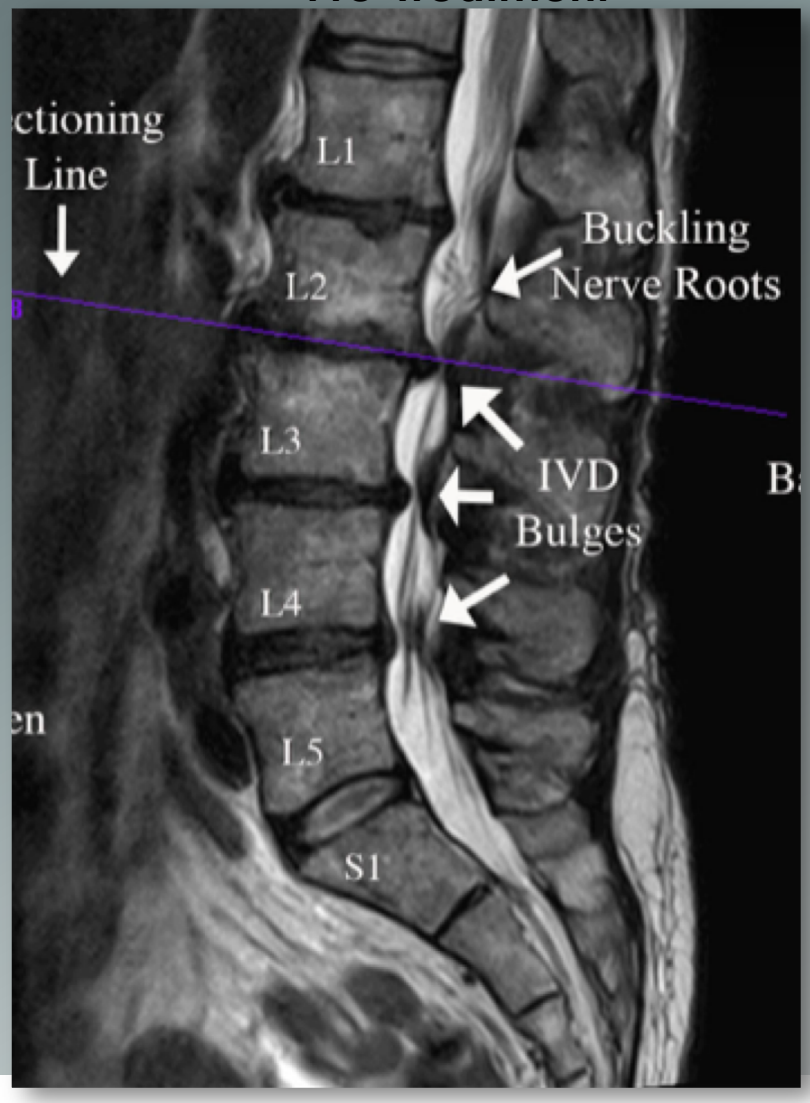
Majority patients reported
significant pain relief at follow-up
(median 9 weeks)

No adverse events reported

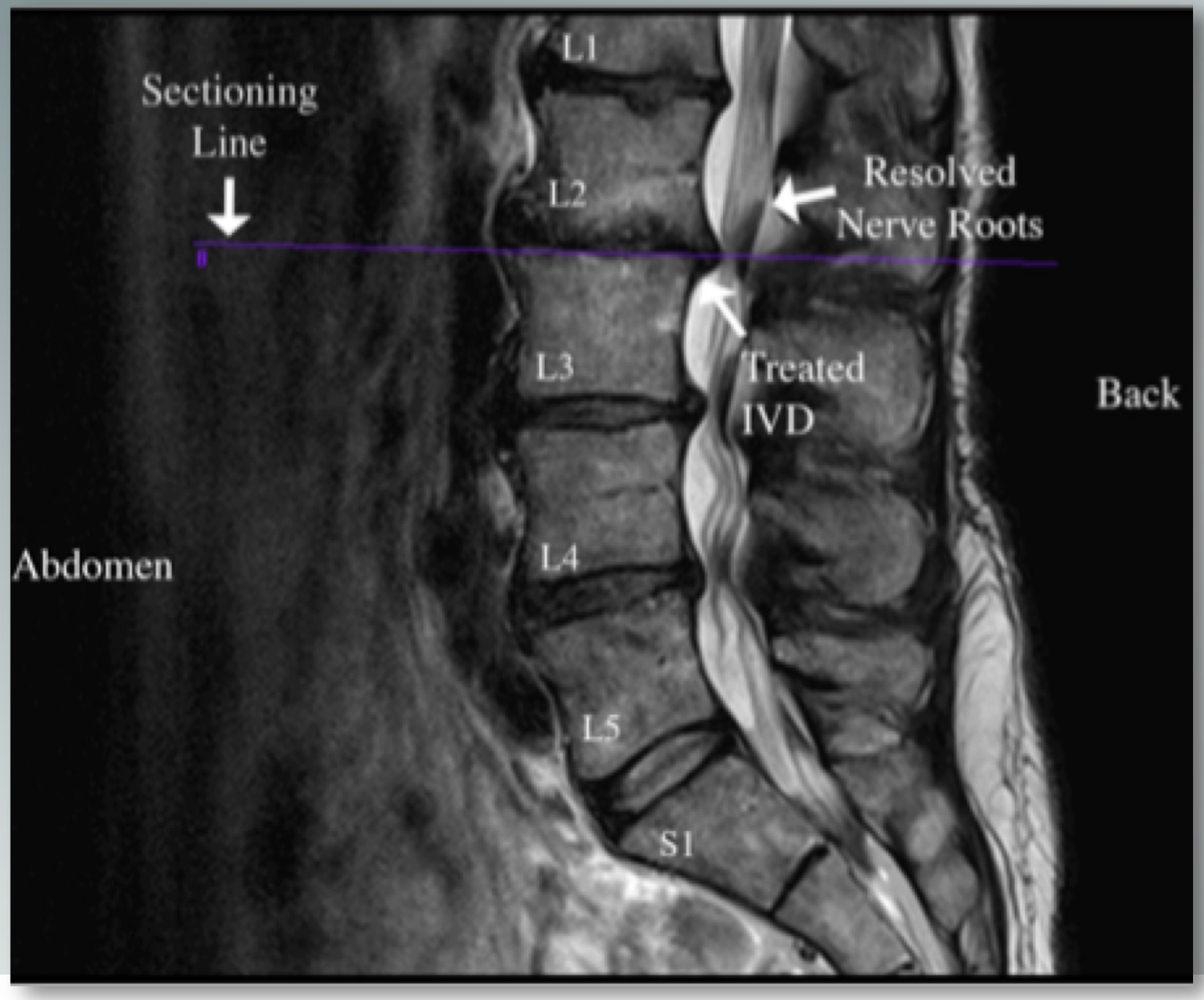


Bone Marrow for Degenerative Disc: Results

Pre-Treatment



Post-Treatment



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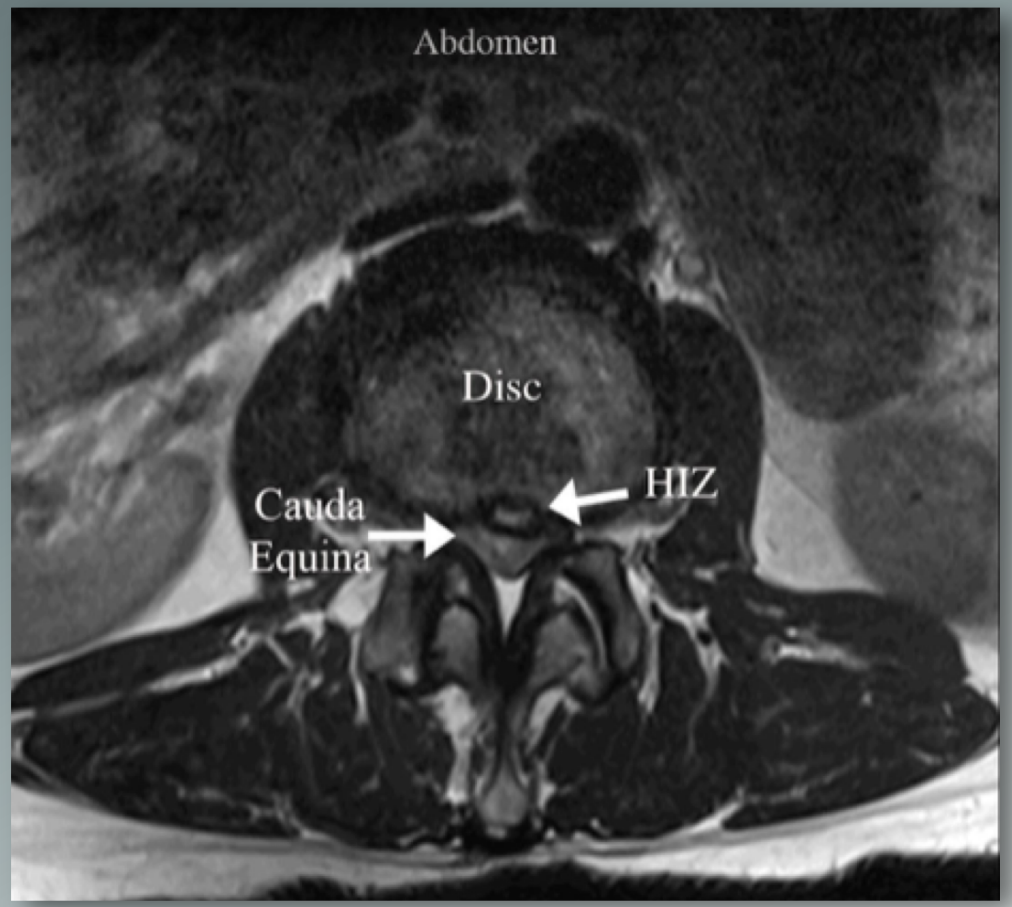
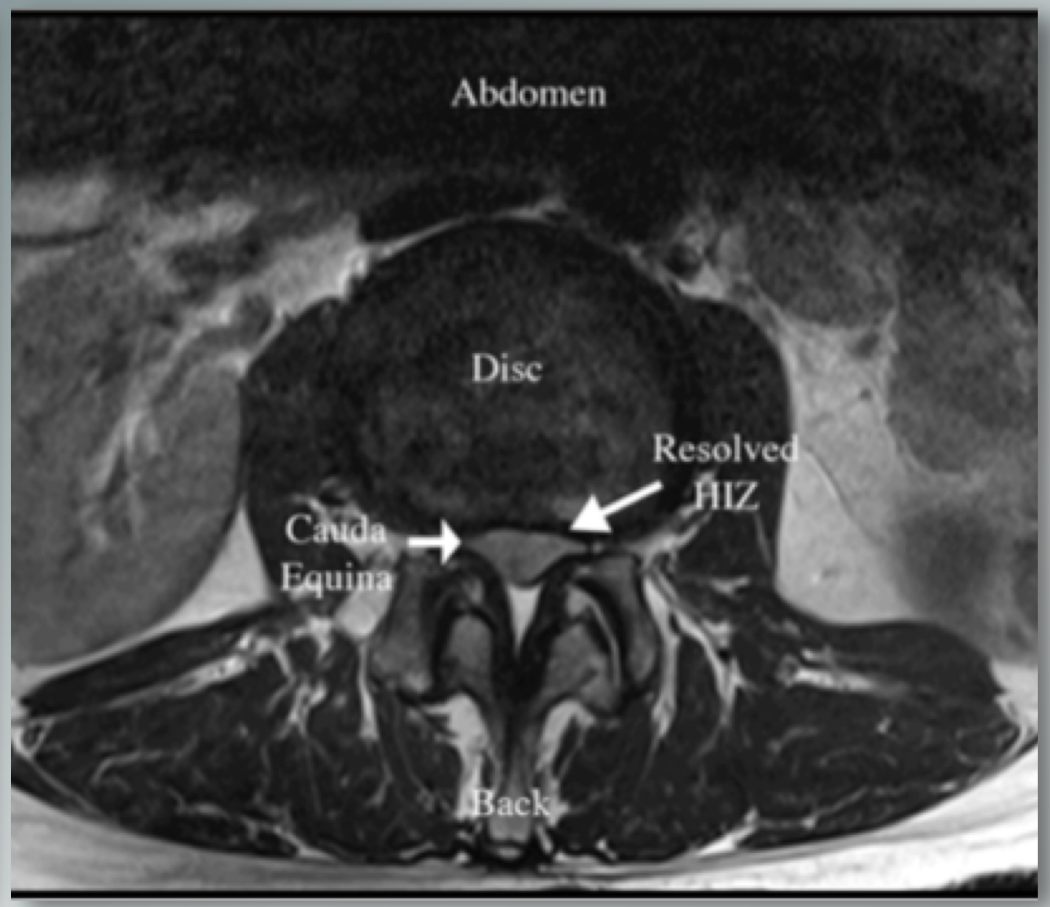
Bone Marrow for Degenerative Disc: Results

Pre-Treatment

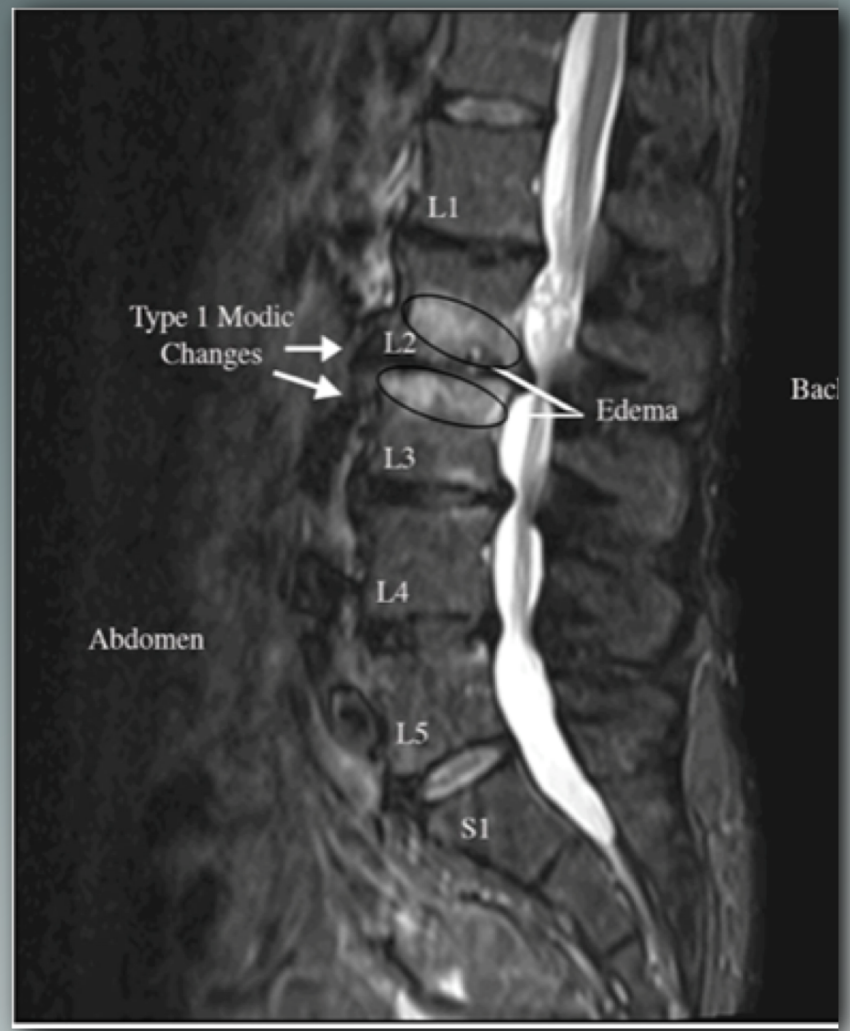


Post-Treatment

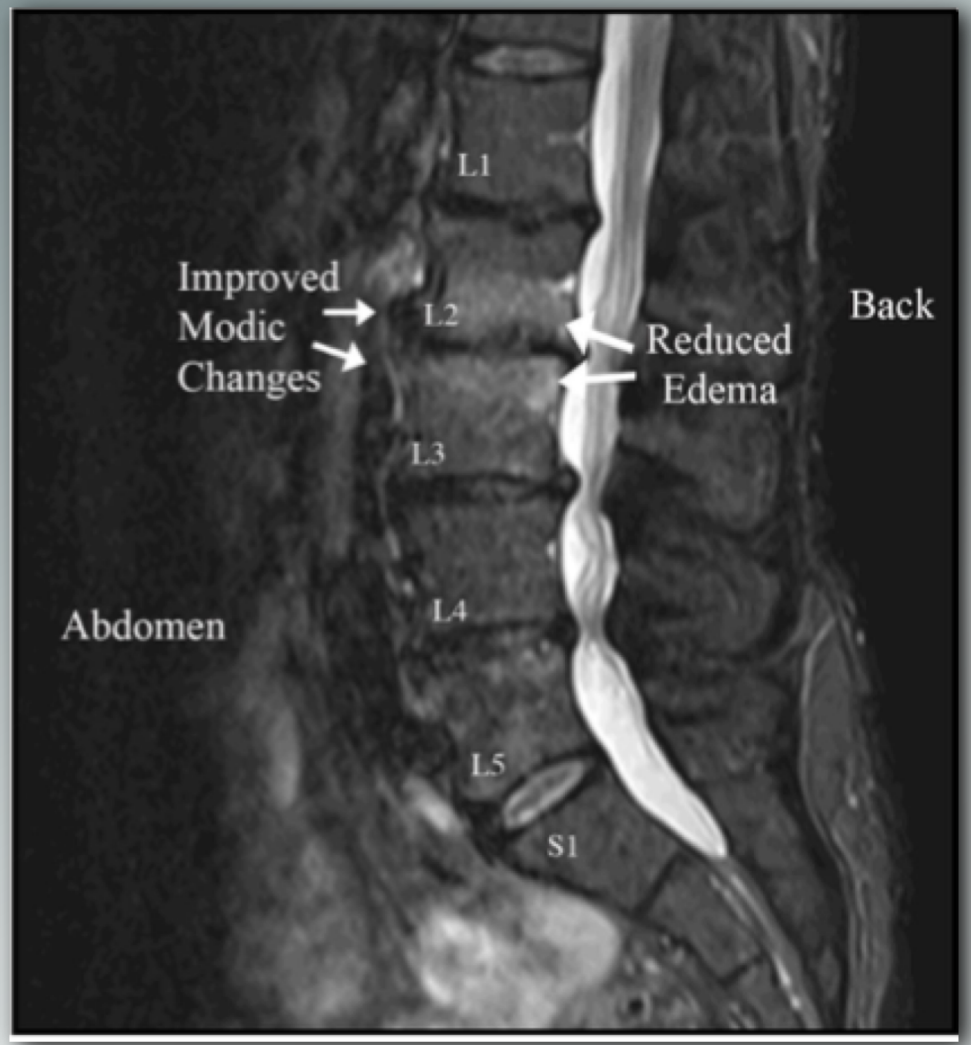


Bone Marrow for Degenerative Disc: Results

Pre-Treatment



Post-Treatment



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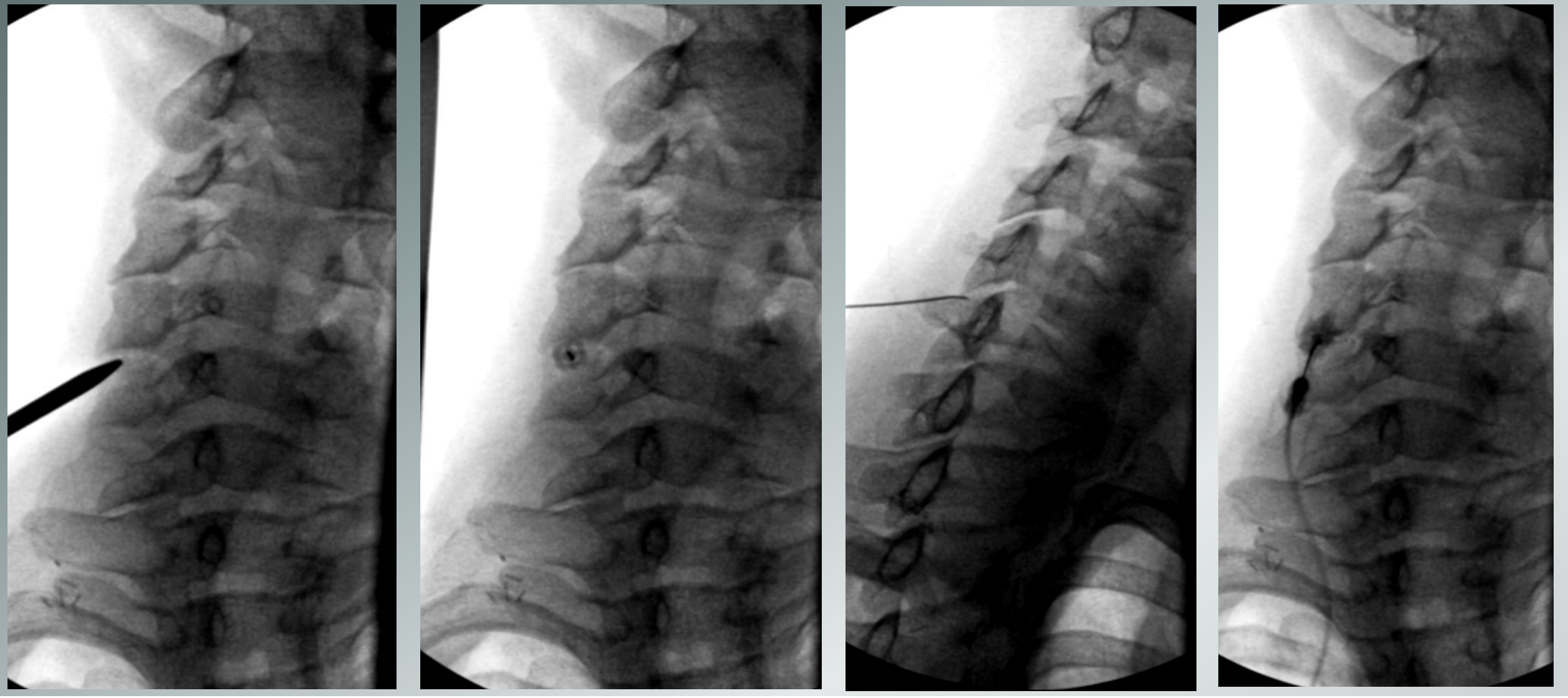
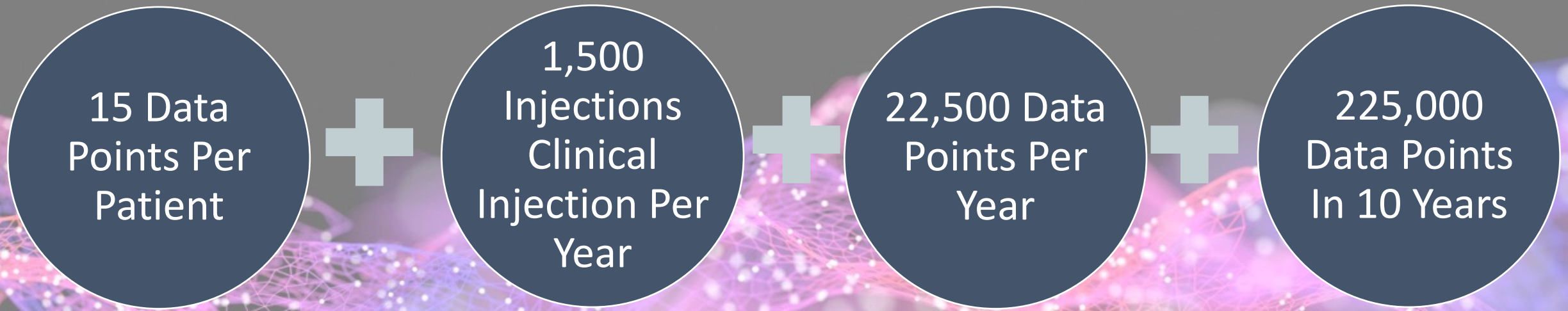
Bone Marrow for Facet Joint Arthritis



The Impact of Biobank Data



The Future of Evidence Based-Biologics

The Good, Bad & Ugly

Inflammation

TGF-β

ILs

Microparticles

VEGF

FGF

PDGF

ROS

MCP

IGF

EGF

IL-1Ra

MMPs

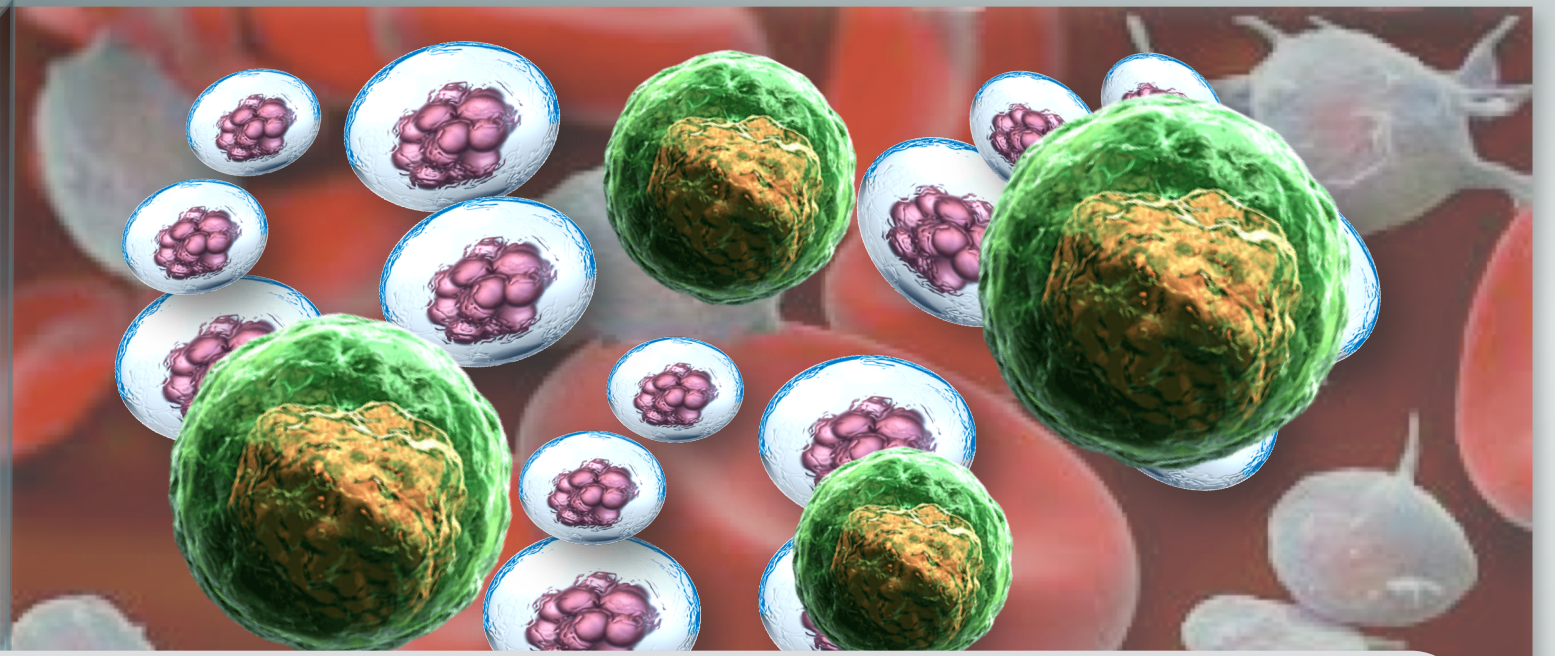
Macrophage proteins

Tissue damage

Matrix degradation

The Good, Bad & Ugly

Senescent Cells



Customizing Bone Marrow Concentrate with FDA Approved Drugs

Improving Bone Marrow Concentrate with Senolytic Compounds

Plant Pigment (flavonoid)

Improve Patient Outcomes

Reduce Senescent Cells

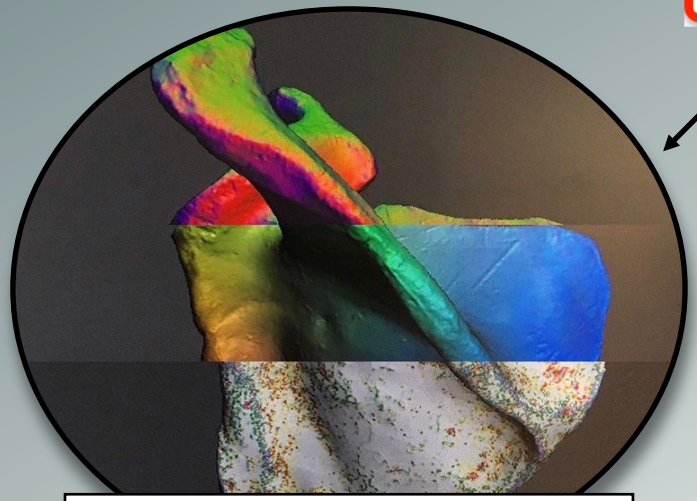
polyphenol from flavonoid group

Research Collaboration

Biomotion & Biomedical Engineering Departments

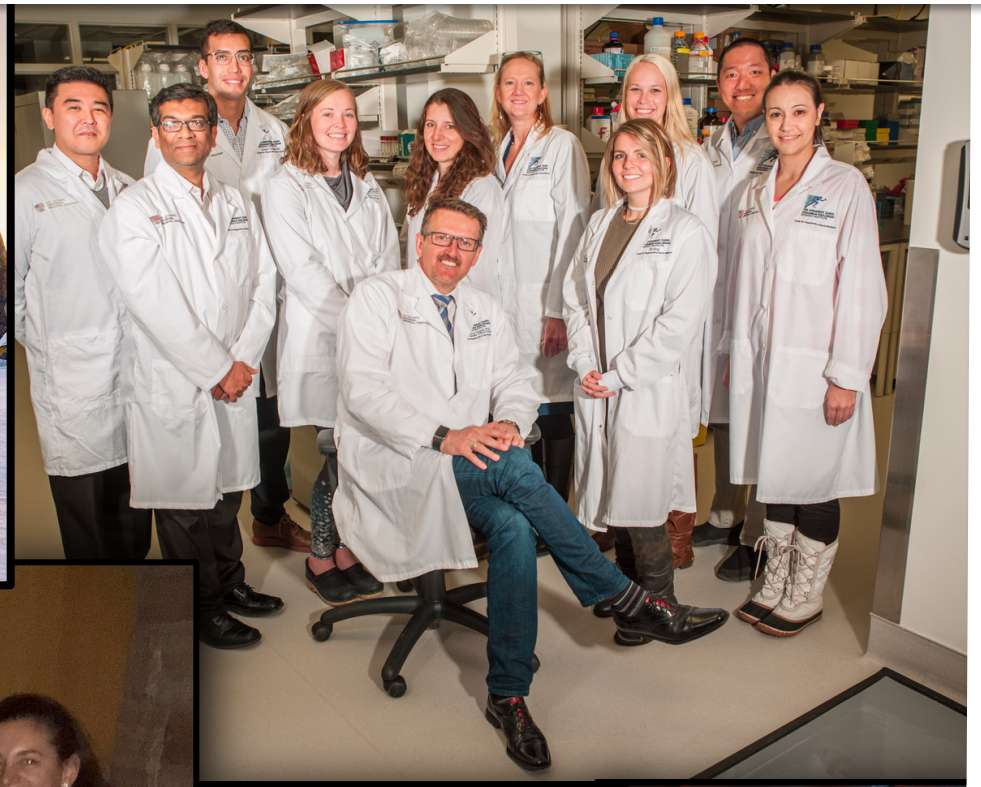
Center for Orthopaedic-Based Outcomes Research

Researching Bone Marrow Concentrate



Imaging Research Department

Center for Regenerative Sports Medicine



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