

# *Non-opioid therapeutic targets:*

Pain in rheumatic and  
musculoskeletal diseases.  
Focus on Osteoarthritis

Anne-Marie Malfait, MD PhD

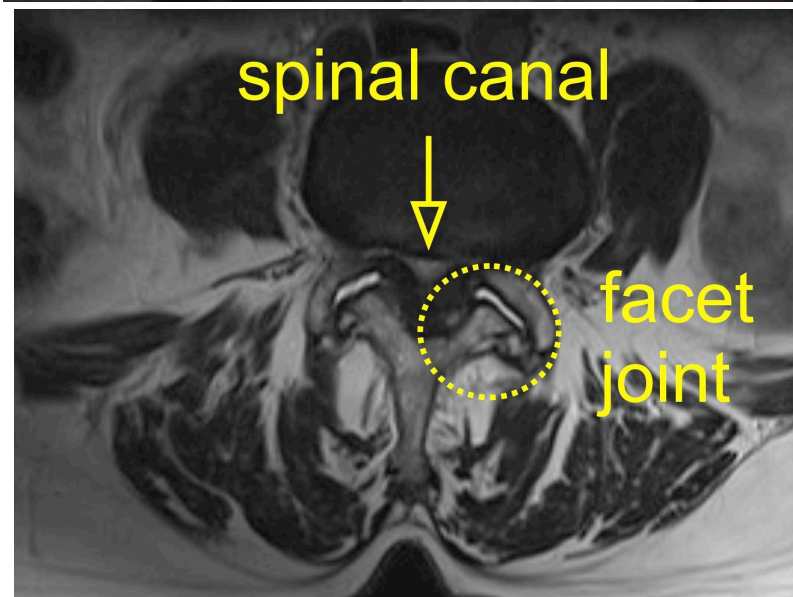
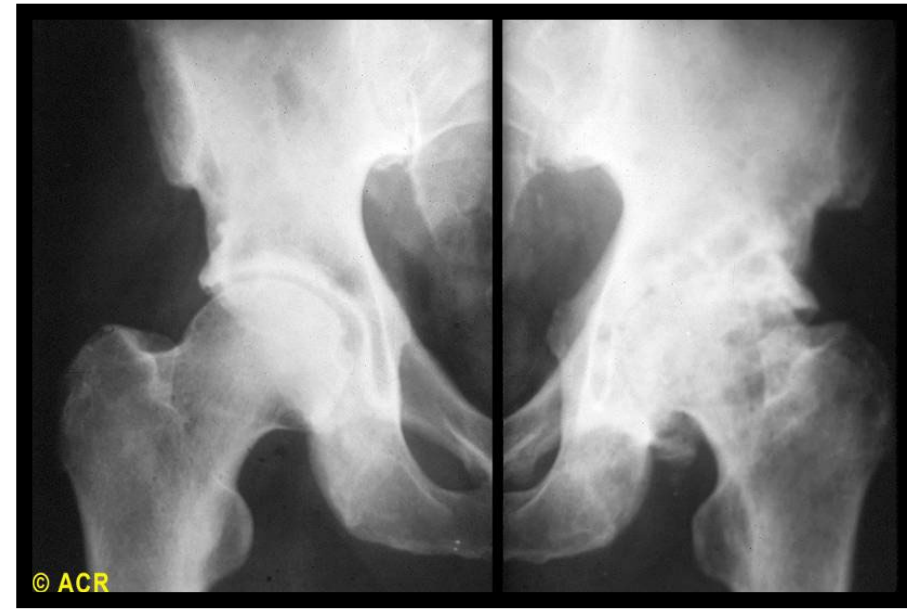
*The Klaus E Kuettnner, PhD, Chair of Osteoarthritis Research*

Division Of Rheumatology, Rush University, Chicago IL



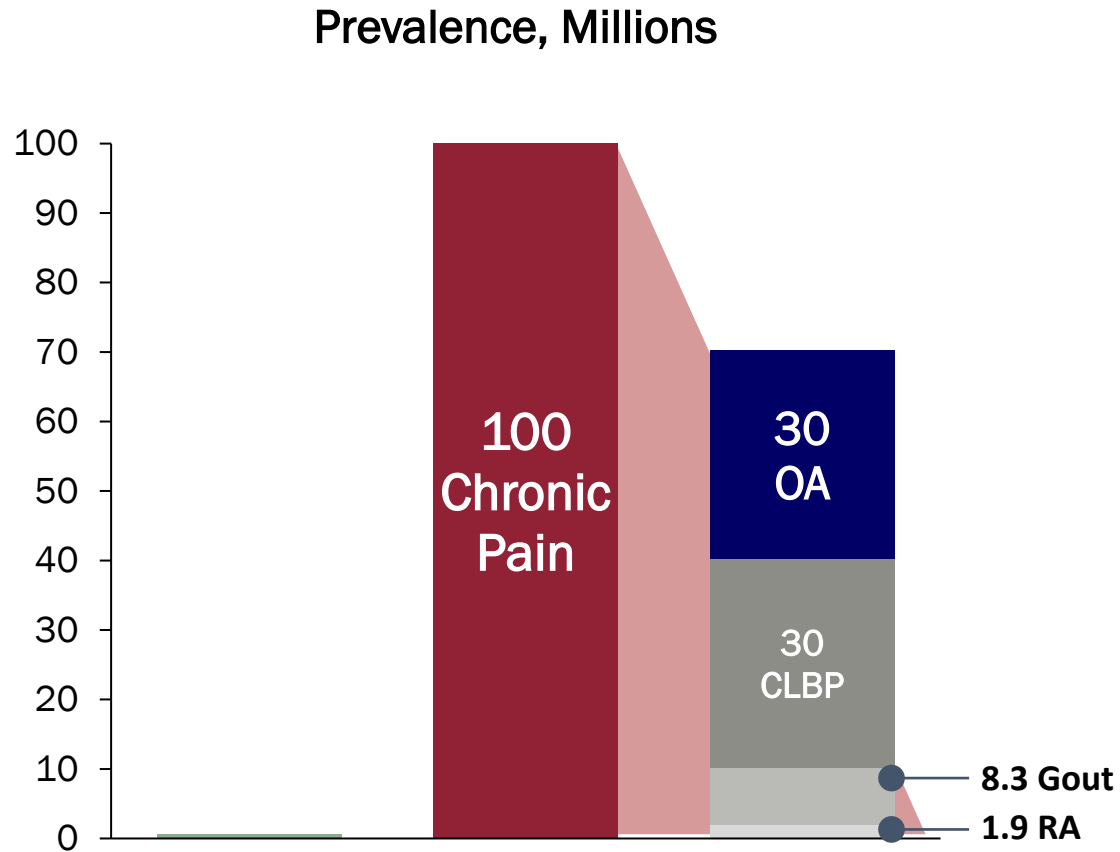
# Osteoarthritis is one of the leading causes of disability and chronic pain in the world

3<sup>rd</sup> most rapidly rising condition associated with disability in the world behind diabetes and dementia



Neogi T, Osteoarthritis Cart 2013;  
Hootman *et al*, Arthr Rheum 2016  
Vos T. *et al*, Lancet 2017 (W.H.O)  
Jin Z *et al*, ARD, 2020

# Chronic MSK Pain is More Prevalent & Costly than Other Common Diseases



- OA affects **600 million** people worldwide
- 3<sup>rd</sup> leading hospital discharge diagnosis in the US reflecting huge total joint arthroplasty prevalence

# The Joint Is An Organ: Multiple Tissues Ensure Its Integrity And Function

## Osteoarthritis Is The Failure Of The Joint As An Organ

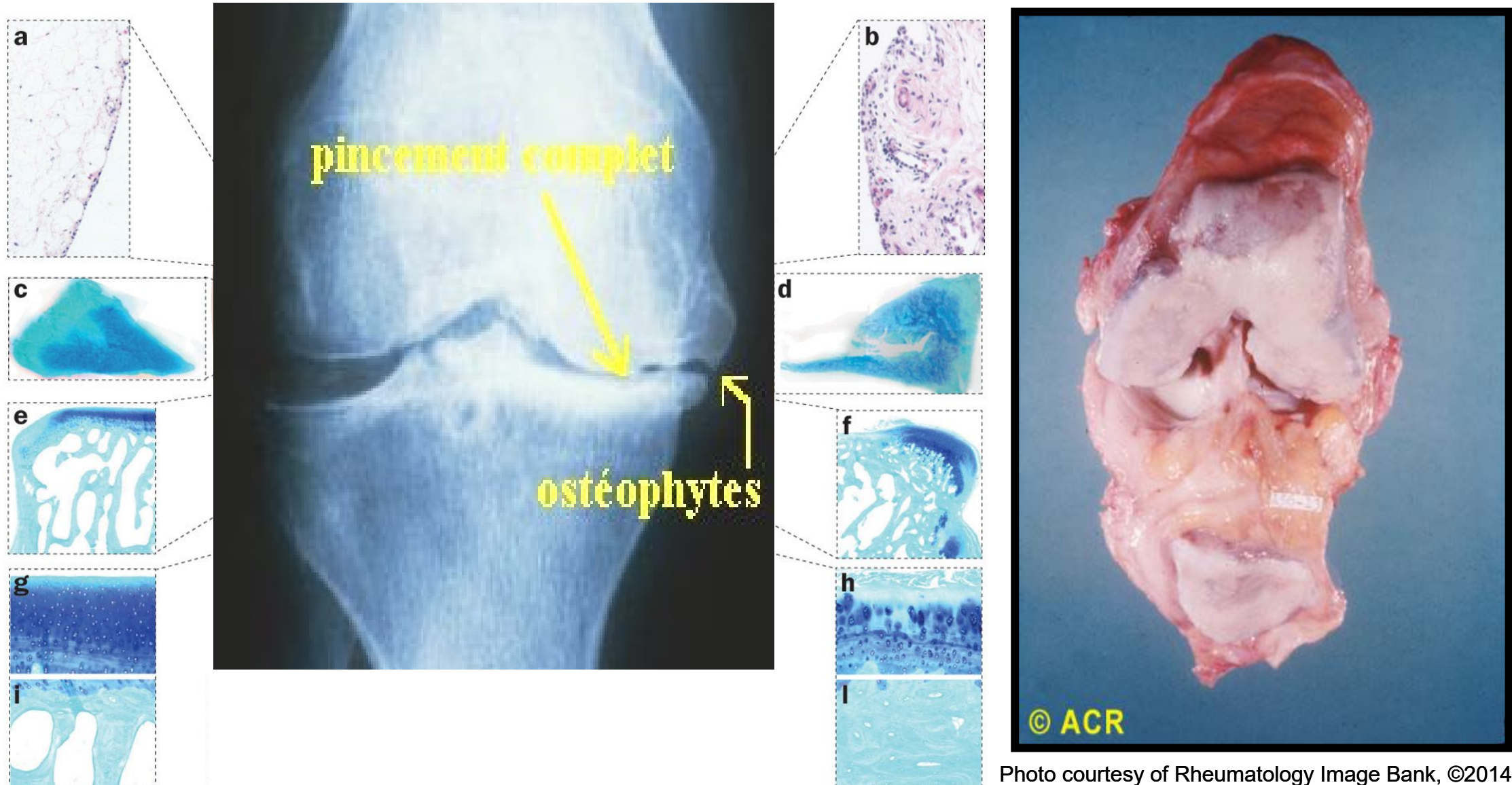


Photo courtesy of Rheumatology Image Bank, ©2014.

# Management Options for this Chronic Condition are Limited

- No treatments to alter structural progression of joint damage.
- Inadequate symptomatic control:
  - Small effect sizes and poor safety of NSAIDs, acetaminophen
  - Opioids are widely prescribed but do not provide sustained pain relief
  - Exercise, weight-loss strategies not optimally implemented

**Joint replacement surgery is considered the definitive treatment**

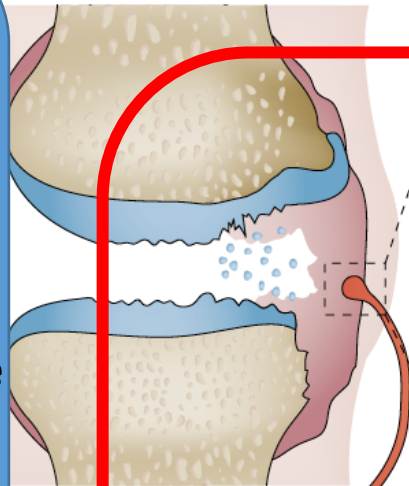
~ 20% have pain/functional limitation post-knee replacement

Wylde V. *et al.* Pain 2011

# Need for mechanism-based approaches in pain management

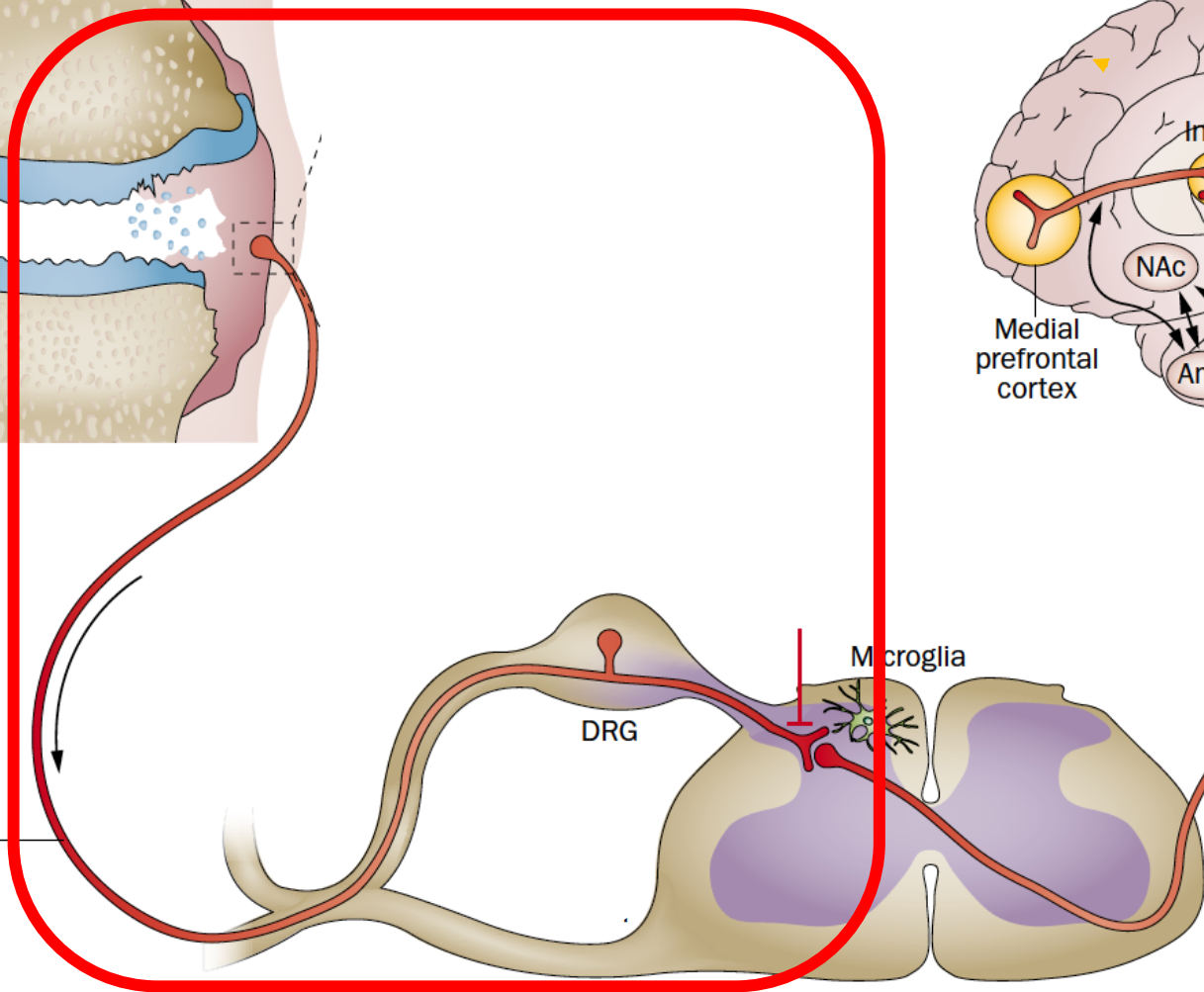
Evidence for a strong peripheral drive in OA pain

Total knee replacement offers pain relief in the vast majority of people (>75%).

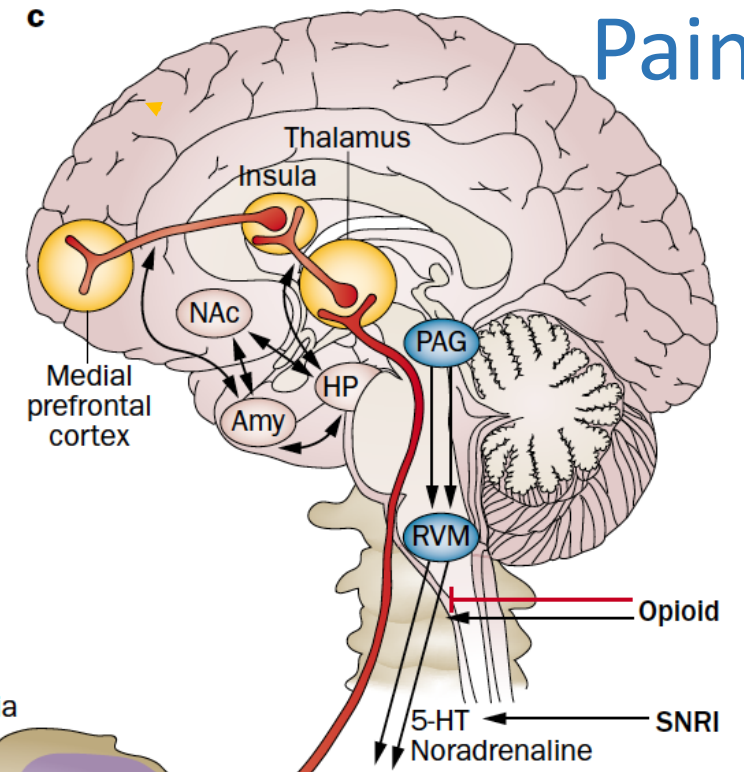


Nociceptor

1. A $\delta$  - fibers (lightly myelinated)
2. C-fibers (unmyelinated – very slow conductors)



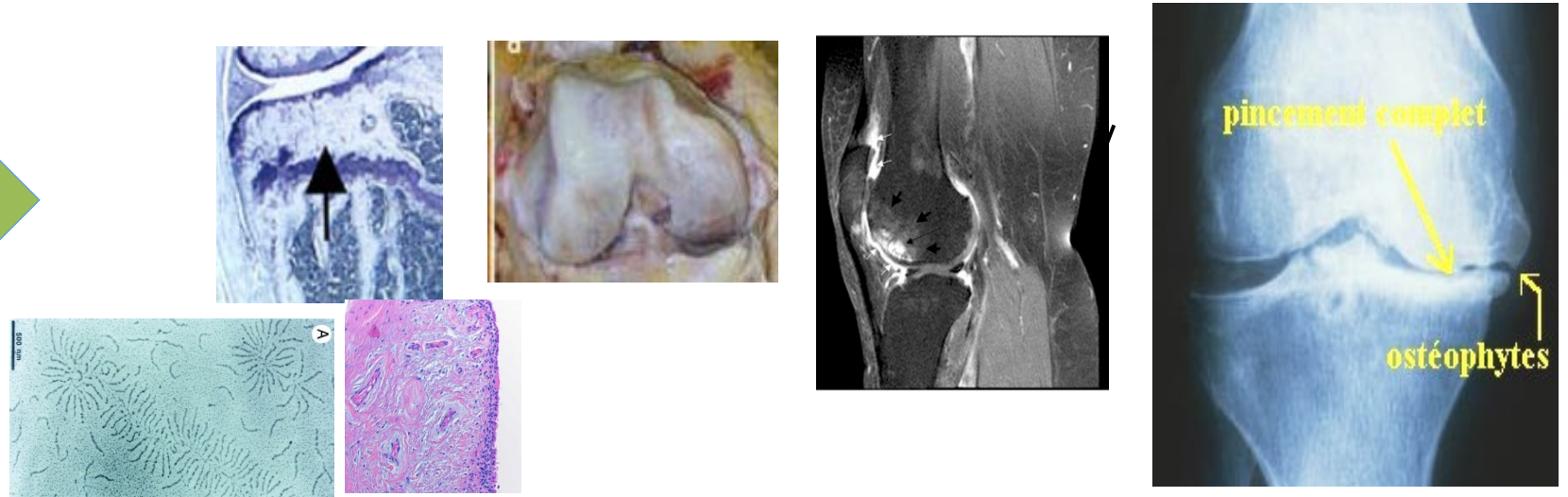
Pain



Opioid  
5-HT  
Noradrenaline  
SNRI

# Osteoarthritis : a chronic progressive pathology that involves all joint tissues

- Mechanical factors (joint alignment, overuse)
- Genetic factors
- Systemic factors (obesity, menopause)



←----- Biochemical/molecular/cellular changes in joint tissues  
STRUCTURAL PROGRESSION (YEARS!) ----->

## PAIN

Insidious onset

Episodic/pain-free periods  
Activity-related  
Mechanical component  
(e.g. pain when climbing stairs)

Neuropathic elements (burning pain)

Neurosensory changes:

- QST: Pain Pressure Thresholds differentiate between OA and healthy controls
- Loss of proprioception & vibratory perception

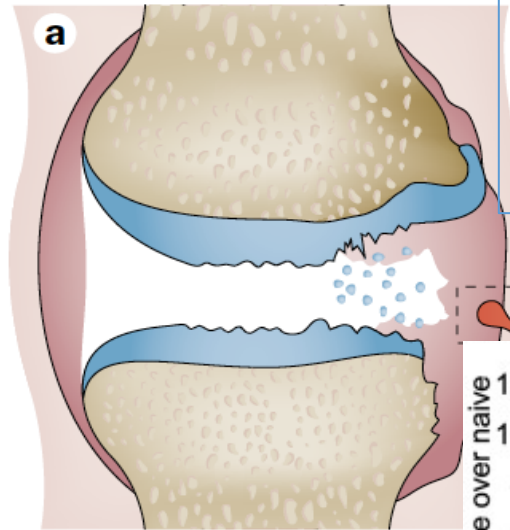
Radiating outside affected Joint

Persistent Pain

Pain at Rest  
Severe flares, at night

- Mechanical factors
- Genetic factors
- Systemic factors (obesity, menopause)

# The (neuro)anatomy of pain in OA – An ever changing landscape

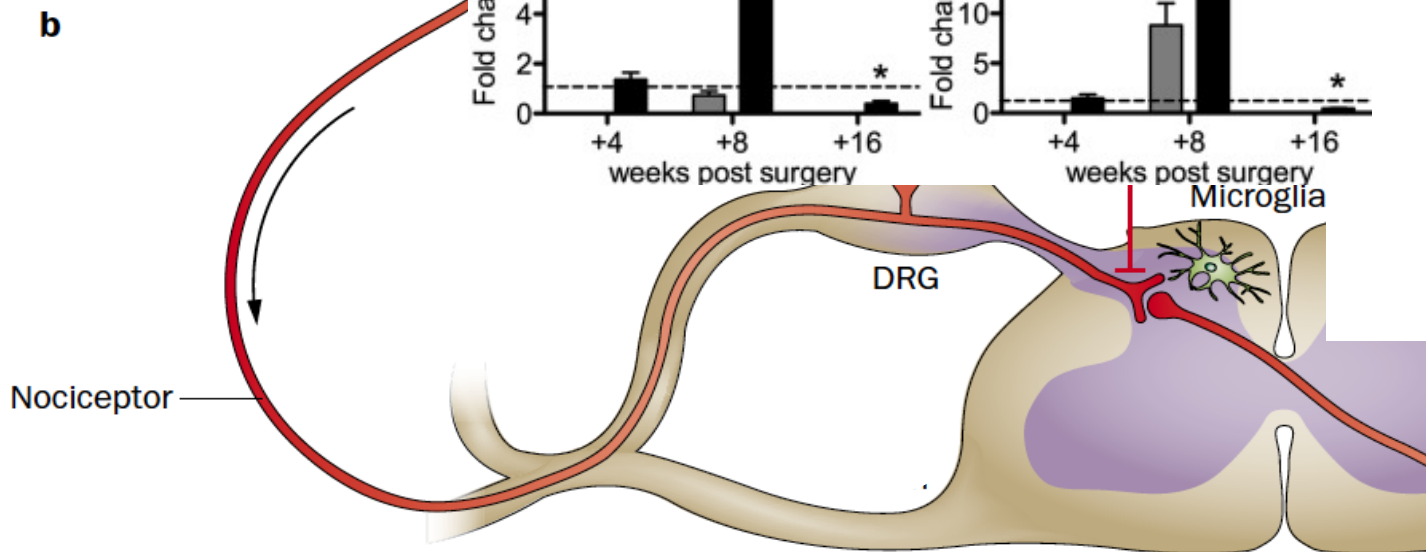
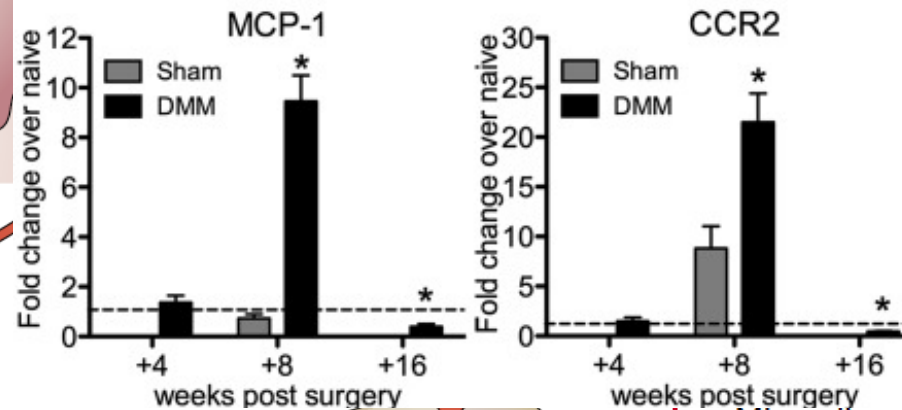


Over time, milieu in the joint changes

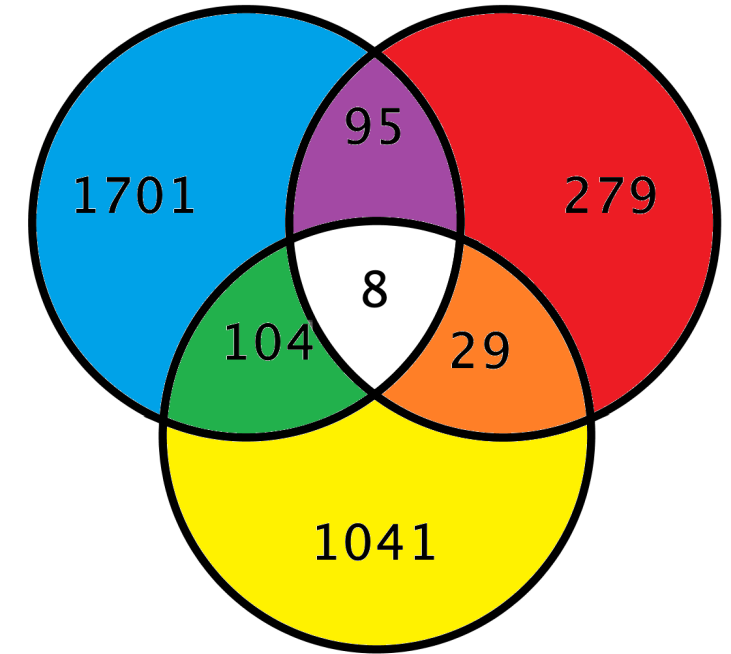
- Synovitis
- Cartilage degradation
- Bone remodeling

Experimental models (4+months):  
Longitudinal changes in pain behaviors

- Early: Sensitization
- Late Weightbearing asymmetry
- Late: Decreased locomotion



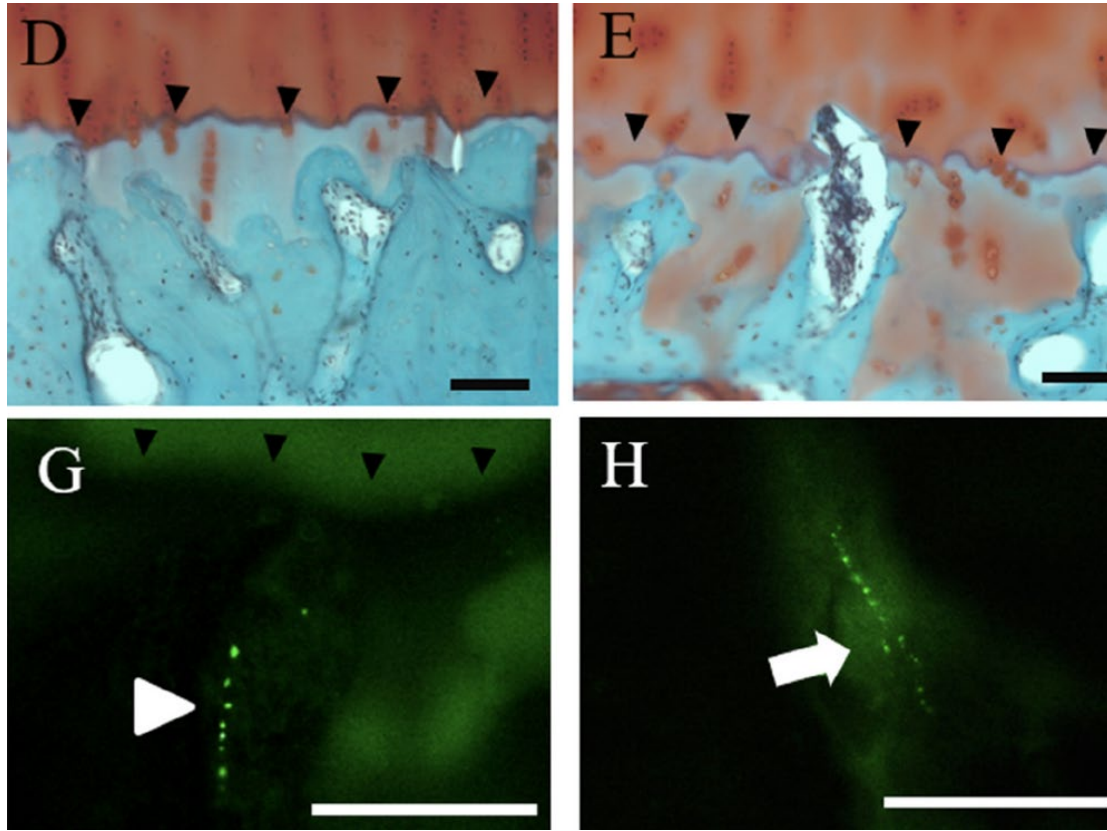
Post-surgical pain      Early OA pain



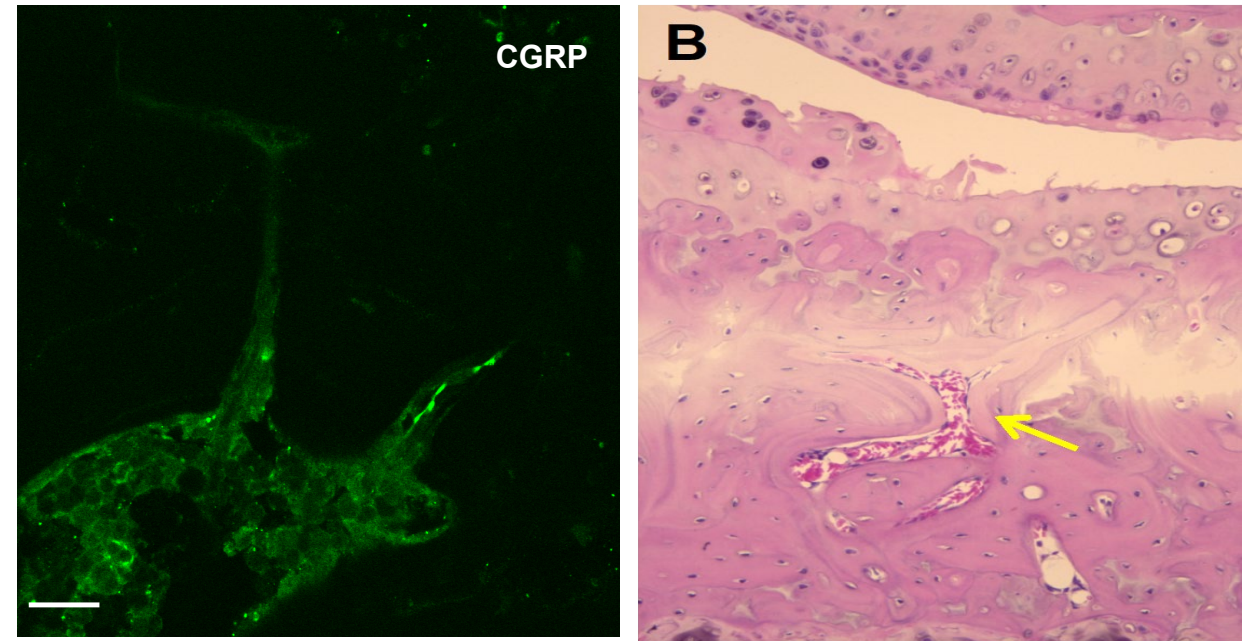
Persistent OA pain



# Sprouting of nociceptors into OA joints: Synovium and Subchondral Bone



Aso K *et al*, Osteoarthritis and Cartilage 2020  
 Subchondral bone in human OA knees:  
 CGRP+ fibers are correlated with pain



Ishihara S *et al*, Arthritis Research & Therapy 2021  
 Subchondral bone in mouse knees after DMM



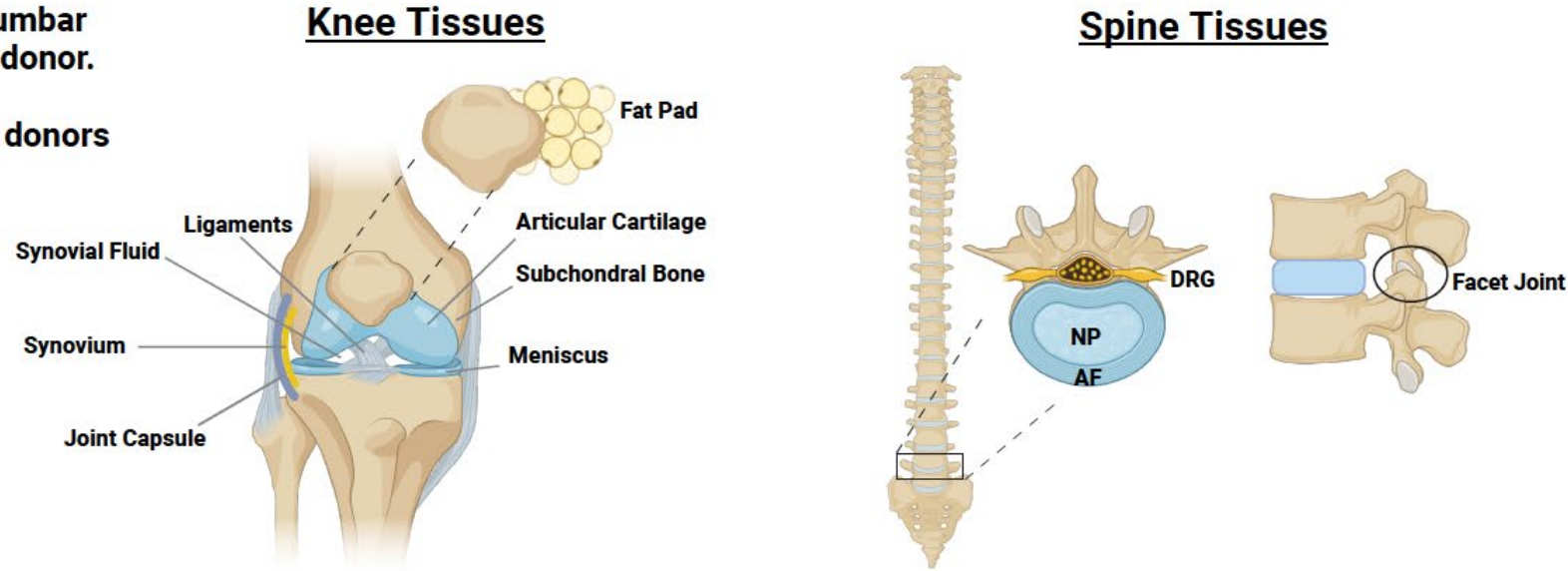
- In 4 models of OA
- DMM
- PMX
- ACLR
- Ageing

Obeidat *et al* 2024

# Discovery of novel mechanisms and molecules involved in OA tissue damage and pain using human tissue collections (Drivers of sensitization and neuroplasticity)

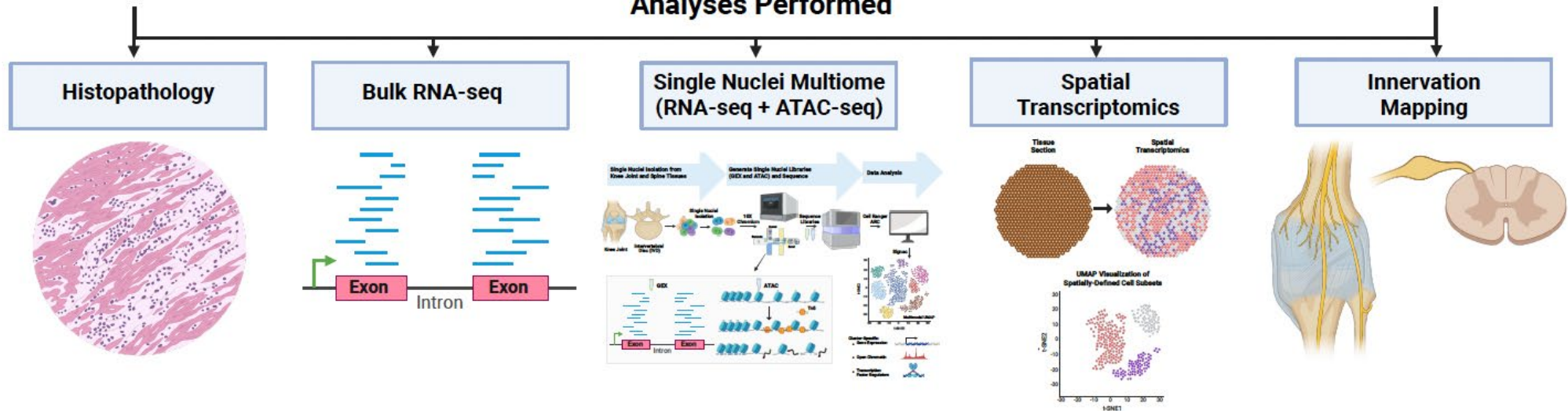
Both knees and lumbar spine from same donor.

Female and male donors age 20-80.



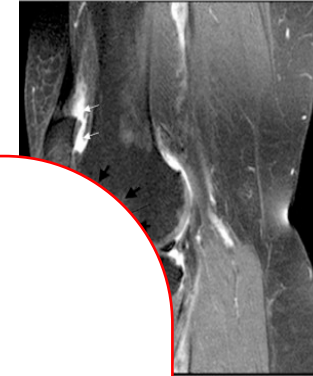
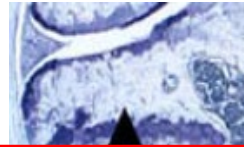
Scripps

## Analyses Performed



# Osteoarthritis : a chronic progressive pathology that involves all joint tissues

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- Genetic factors
- Systemic factors (obesity, menopause)



**Discordance between radiographic OA and pain**

**PAIN**

**Effect of analgesia on joint damage**

- “analgesic hip” (NSAIDs)
- rapidly progressive OA in patients who received anti-NGF

Radiating outside affected Joint

Insidious onset

Episodic/pain-free periods  
Activity-related  
Mechanical causes  
(e.g. pain when walking)

Neuropathic elements (burning, tingling)  
Neurosensory changes:

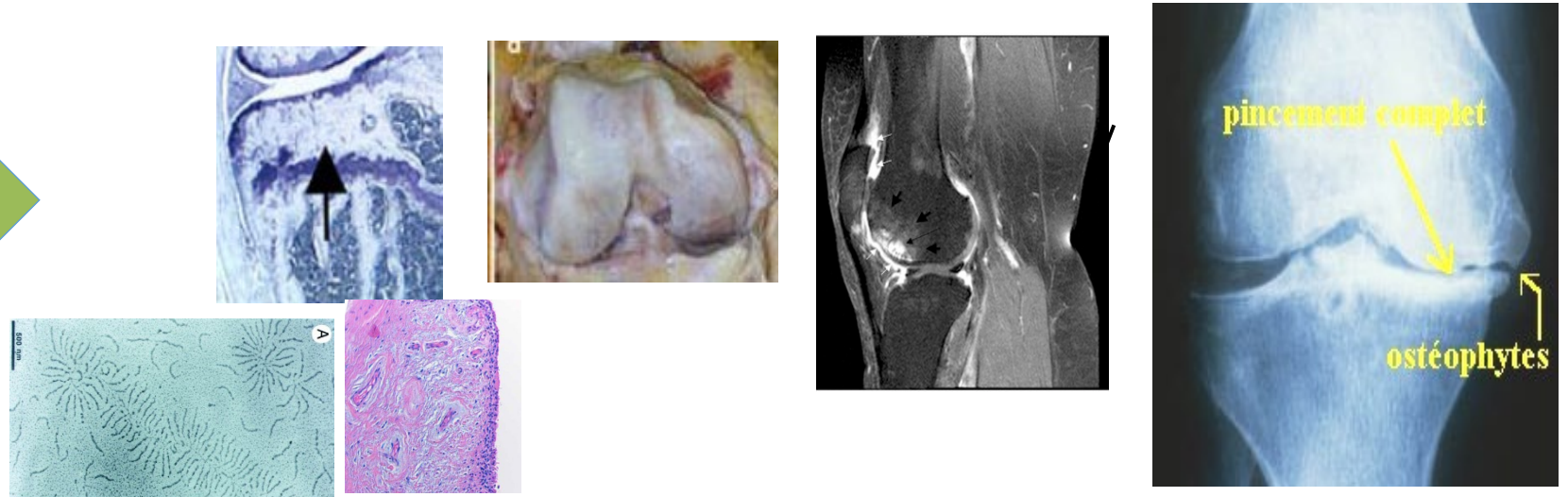
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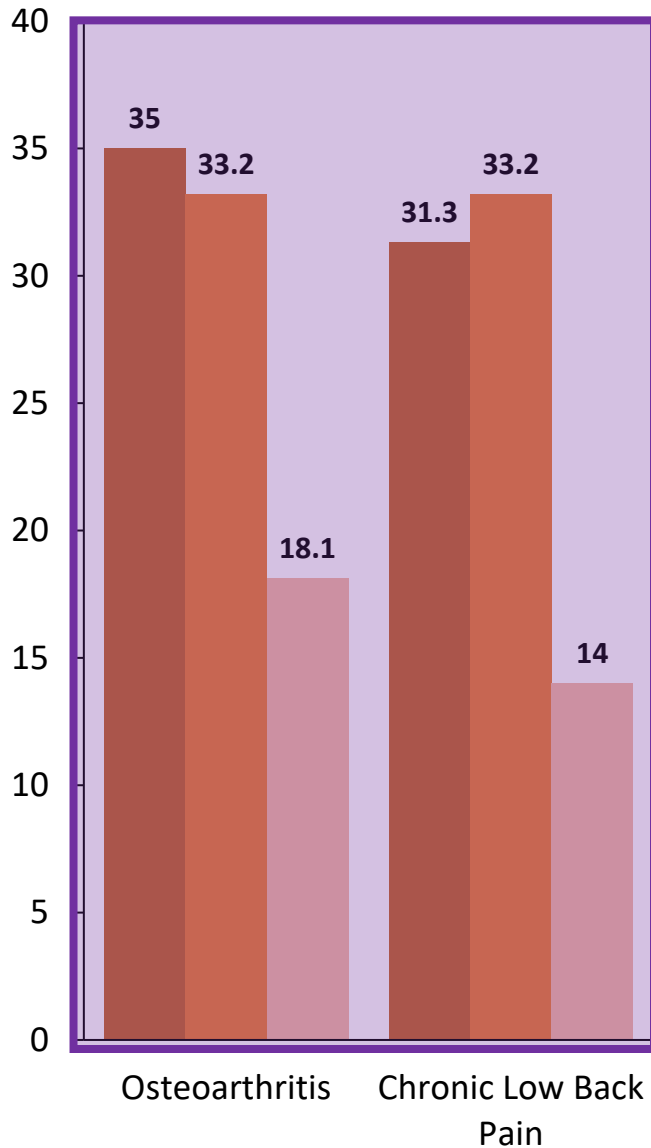
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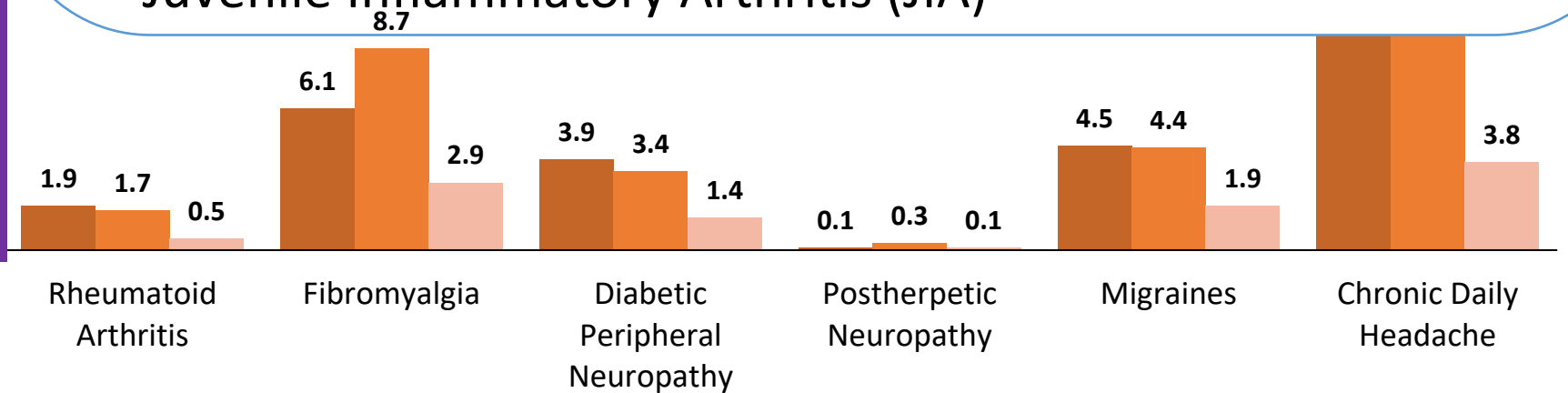
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- Osteoarthritis in other joints, and TMJ
- Rheumatoid Arthritis:
  - Despite major advances in the treatment of inflammation in arthritis, many people continue to suffer distressing chronic pain. Non-inflammatory mechanisms are increasingly recognized in people with inflammatory arthritis.
- Spondyloarthritis – inflammatory low back pain in axial SpA
- Inflammatory myopathy
- Tendinopathy (achilles tendon)
- Ehlers Danlos Syndromes and other Hereditary Connective Tissue Diseases
- Juvenile Inflammatory Arthritis (JIA)



\*Estimated projections.



 **NIAMS** National Institute of Arthritis and  
Musculoskeletal and Skin Diseases  
National Institutes of Health, Department of Health and Human Services

 **RE-JOIN**

<https://mskpain.center>

