Challenges with Assessment of Disease Progression (15 min): Clinical and Structural

Tim McAlindon MD MPH

Tufts Medical Center, Boston

Conflict of Interest Disclosure

Grant Funding

- NIH, FDA

Ad Boards

- Pfizer / Lilly, Samumed, Regeneron, Astellas, KolonTissueGene, Novartis, Remedium-Bio, UCB

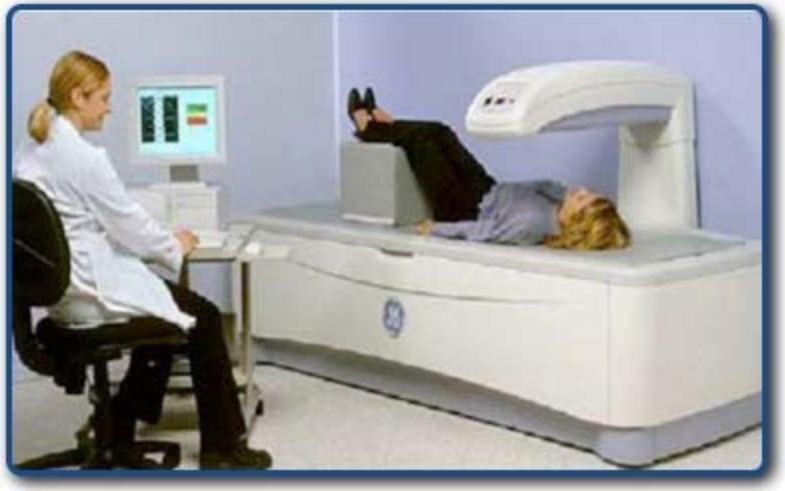
Corporation

- Ambulomics, Arthrometrics

OA Reality Check: The Osteoporosis Analogy

- Common age-related MKS disorder
- Yet Multiple treatments

- AGEISM
- Measurement technology gaps
  - **No ‘DXA’ for OA**

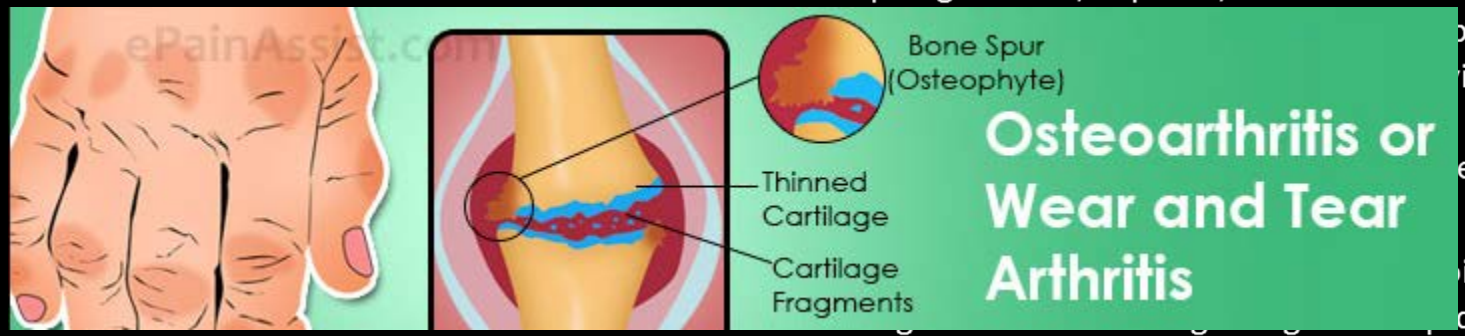


- Heuristic errors

Historical perspective: OA in the 20th century

Risk Factor Profile

- Old Age
- Overweight
- Joint injury
- occupational (heavy, injurious) joint use
- Heritability
- Estrogen withdrawal (menopause



Primary or idiopathic

Localized

- Hands: e.g. nodal OA, erosive OA, first CMC joint OA
- Feet: e.g. hallux valgus, hallux rigidus, talonavicular OA
- Knee: e.g. patello-femoral syndrome, medial/lateral compartment OA
- Hip: e.g. diffuse, superior, concentric

oral joints, apophyseal joints
icular, temporomandibular

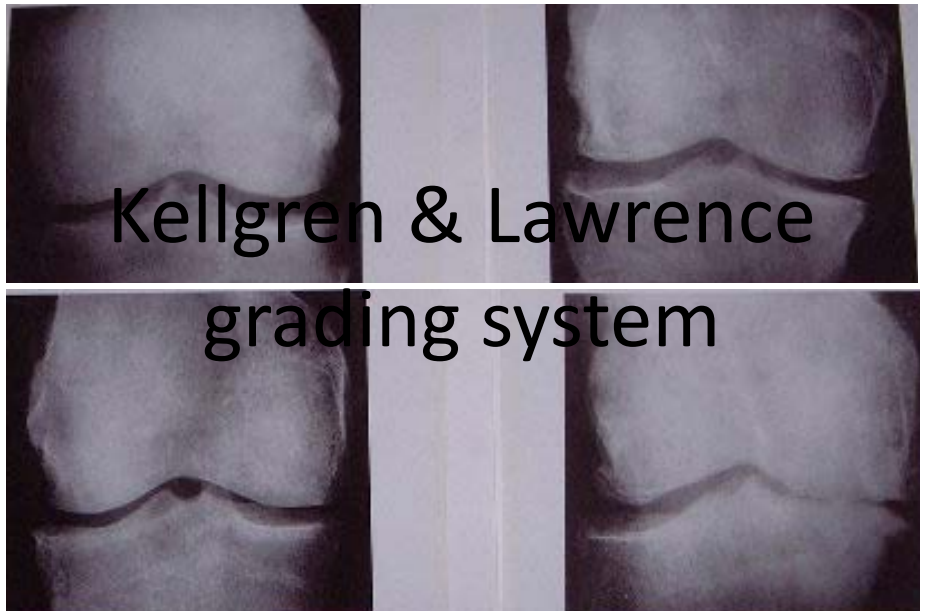
e

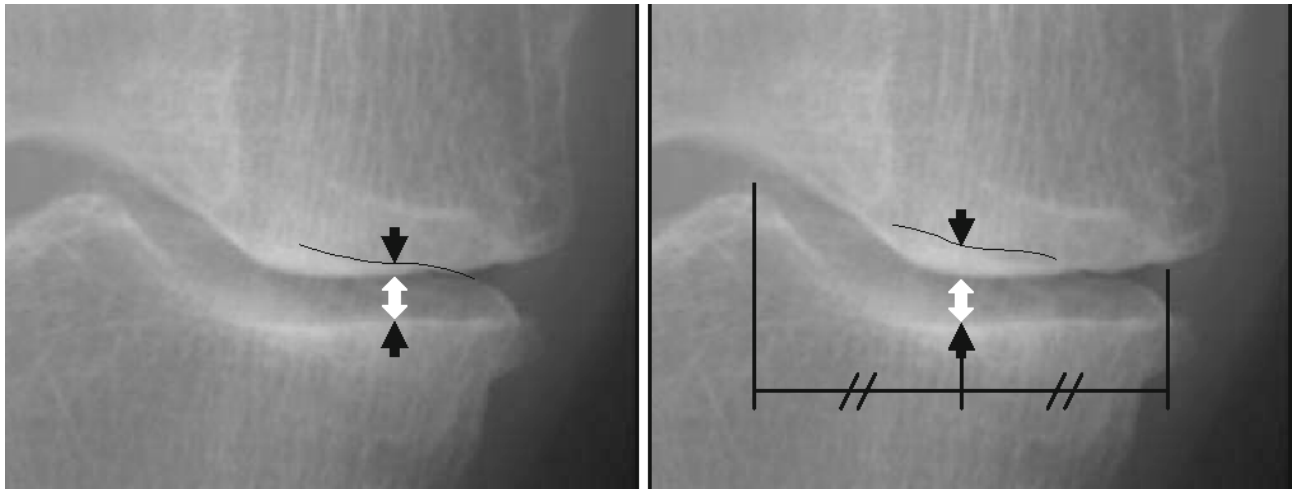
int surgery
dislocation, chondral dysplasia

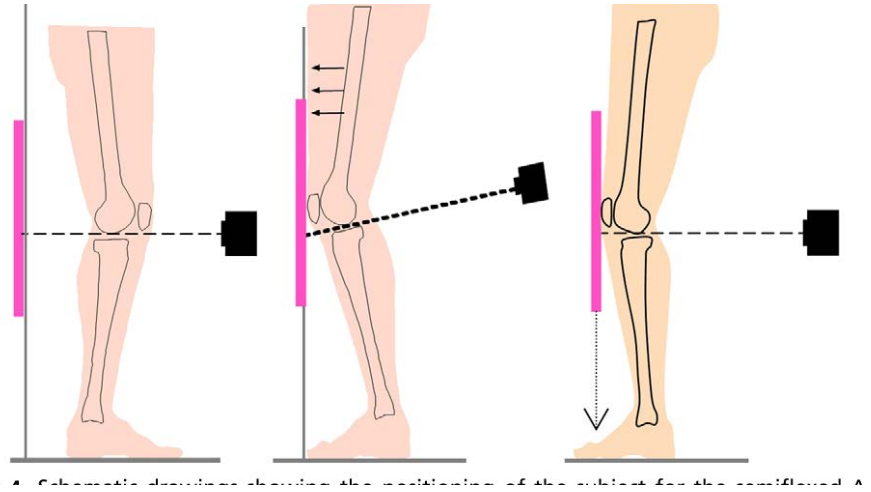
- Metabolic
- Calcium crystal deposition
- Haemochromatosis
- Acromegaly
- Paget's disease
- Ochronosis
- Inflammatory
- Septic arthritis
- Avascular necrosis
- Neuropathic; charcot joints

OA in the 20th century

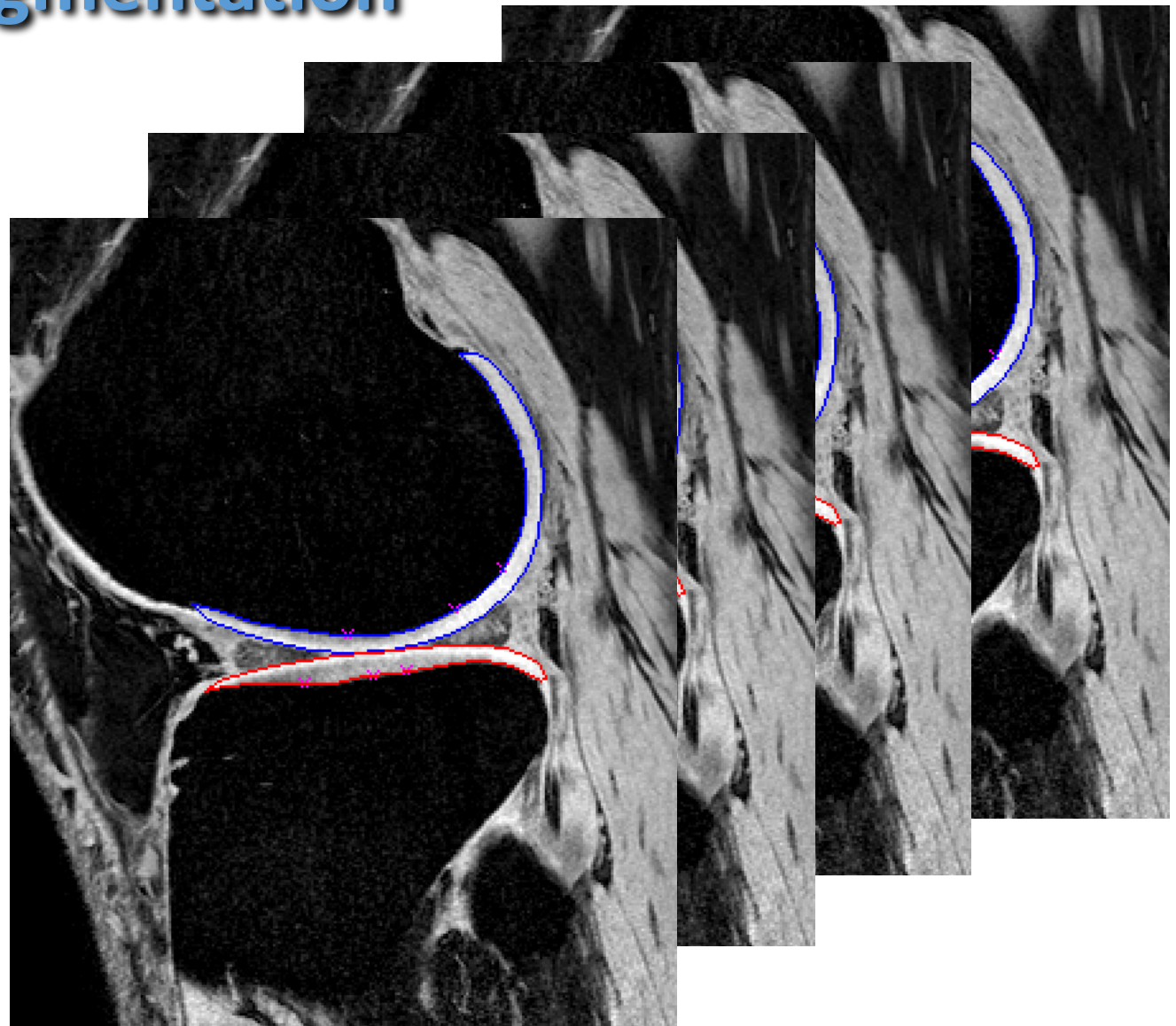
OA = cartilage *degeneration*





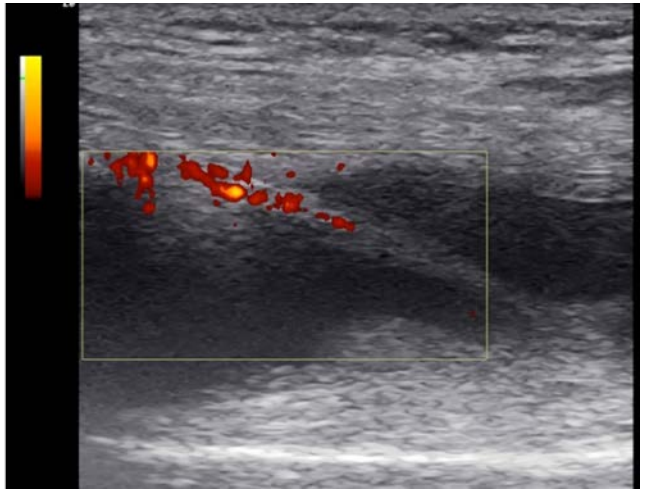


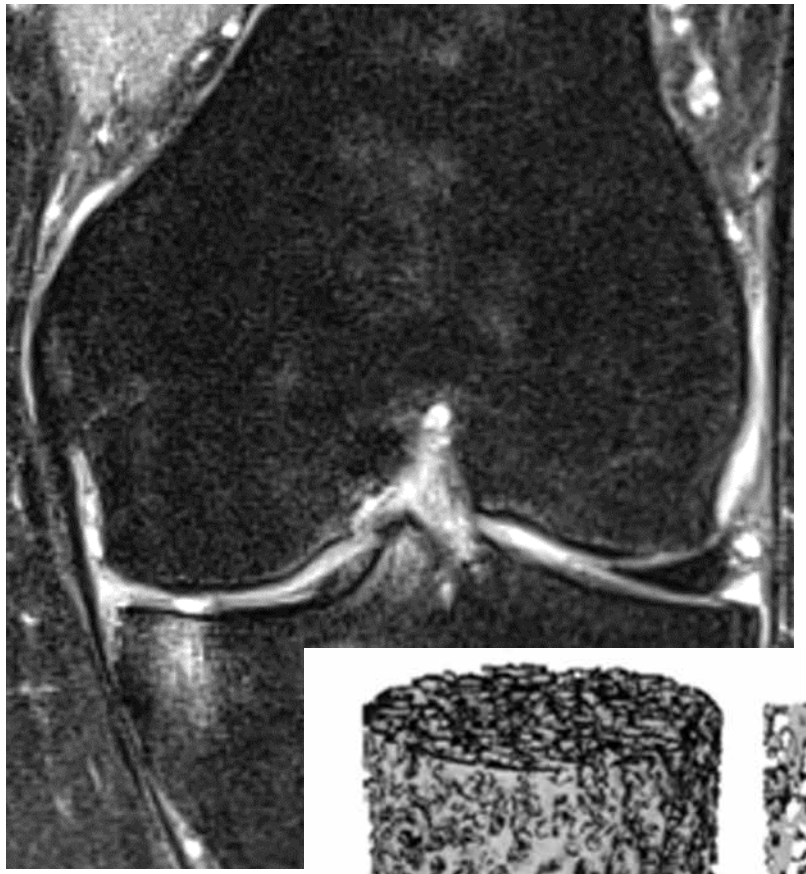
OA: Imaging Biomarker Development
Cartilage Segmentation



OA development in late 20th / early 21st C

- Imaging
- Biopsies
- Clinical studies
- Epidemiology
- Biomechanical





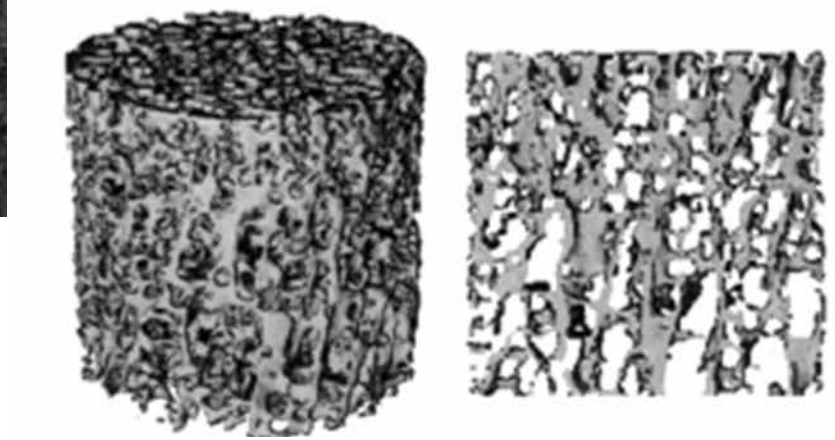
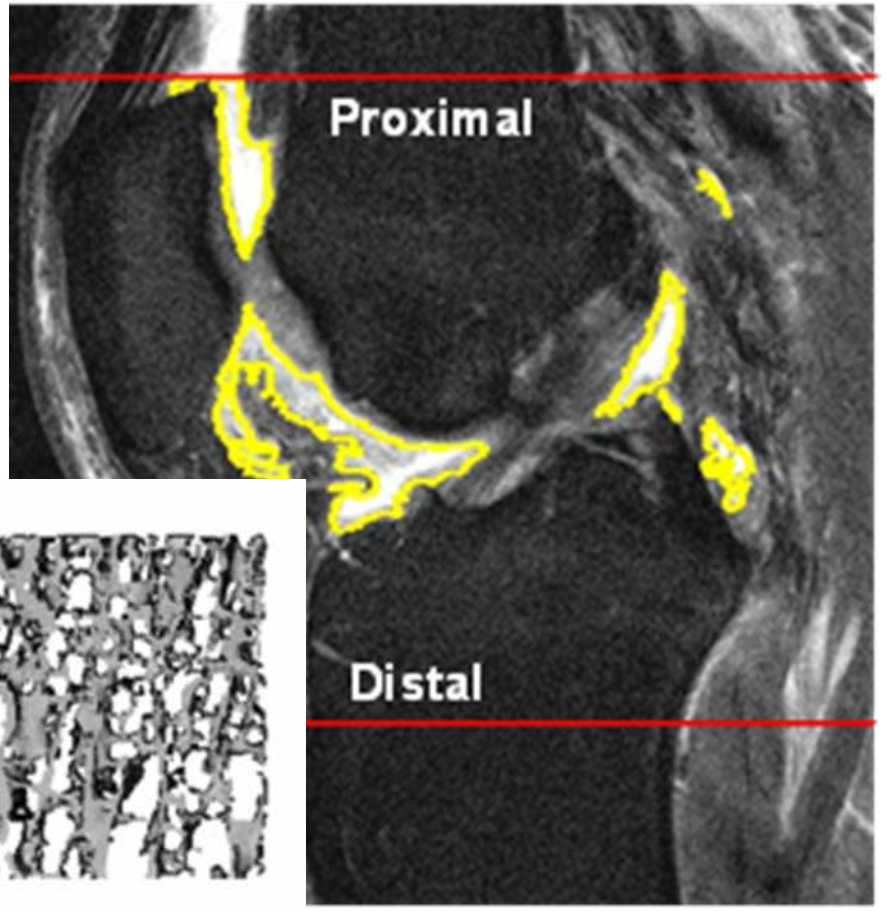


Figure 8. Example of joint effusion-synovitis volume segmentation (red lines demarcate the region of interest, yellow indicates regions of effusion).



Heuristic evolution of OA pathogenesis

EDITORIAL

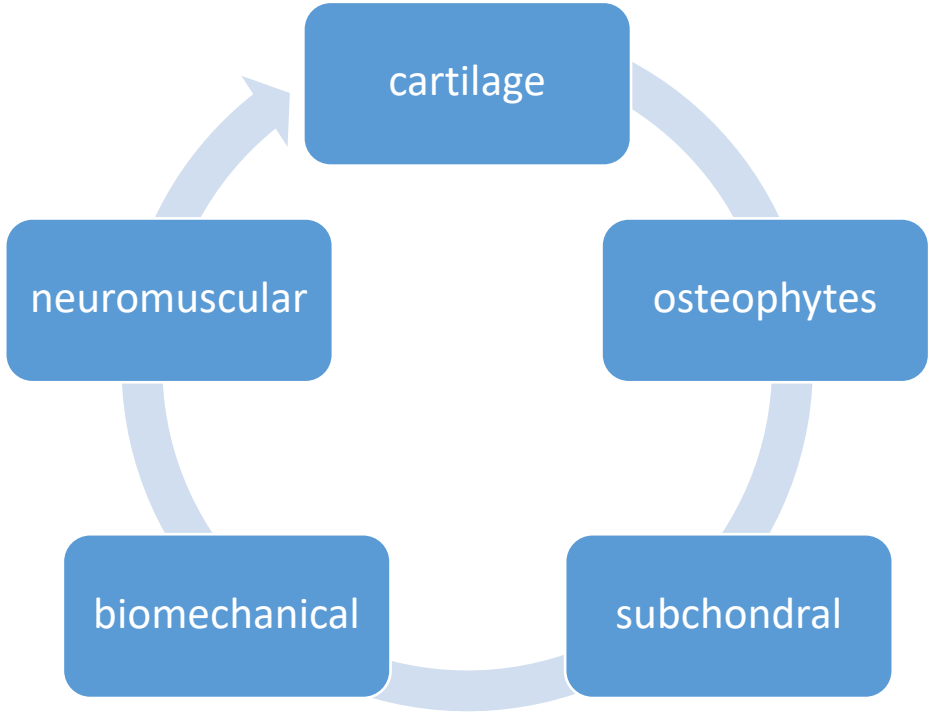
Osteoarthritis is not a cartilage disease

Yet more evidence that osteoarthritis is not a cartilage disease

K D Brandt, E L Radin, P A Dieppe, L van de Putte

ARD 2006

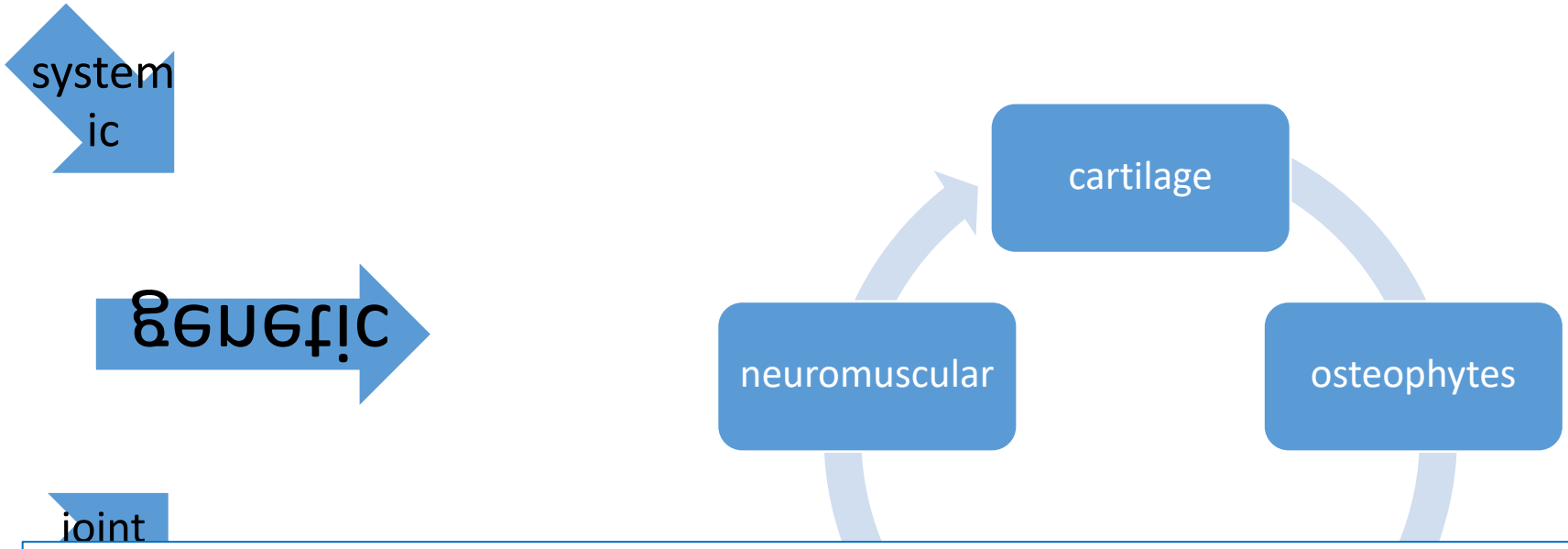
OA: *whole joint* disorder

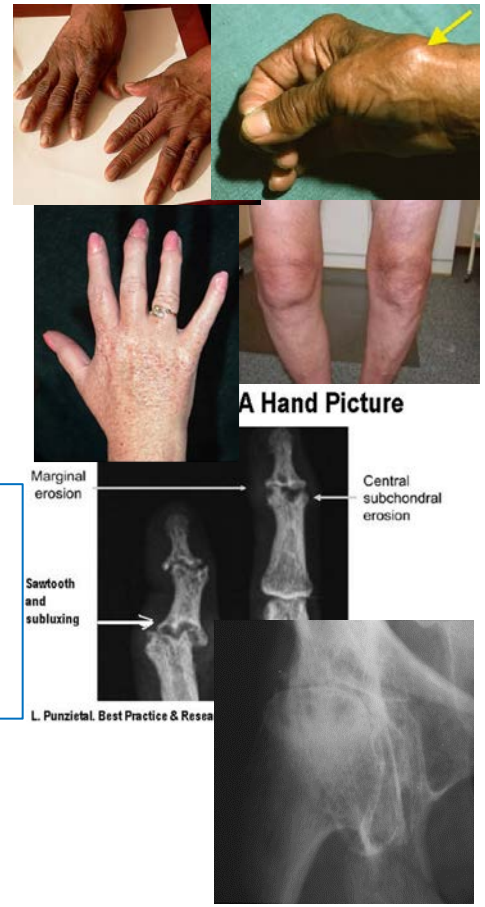


- "OA is not a cartilage disease"
- "multifactorial and complex etiopathogenesis" - FDA
- OA as *joint failure*

Heuristic evolution of OA pathogenesis

Multiple pathways | ***whole joint* disorder** | ***wide-ranging clinical appearances***





Need for an overall conceptual model that integrates the numerous pathophysiologic pathways to OA in a joint with the plethora of clinical manifestations in a way that suggests potential treatment targets

Definition of *disease*

…a condition of the living animal …or of one of its parts that impairs normal functioning and is typically manifested by distinguishing signs and symptoms : sickness, malady

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distinguishing signs

- clinical
- radiographic
- MRI

traditional paradigm

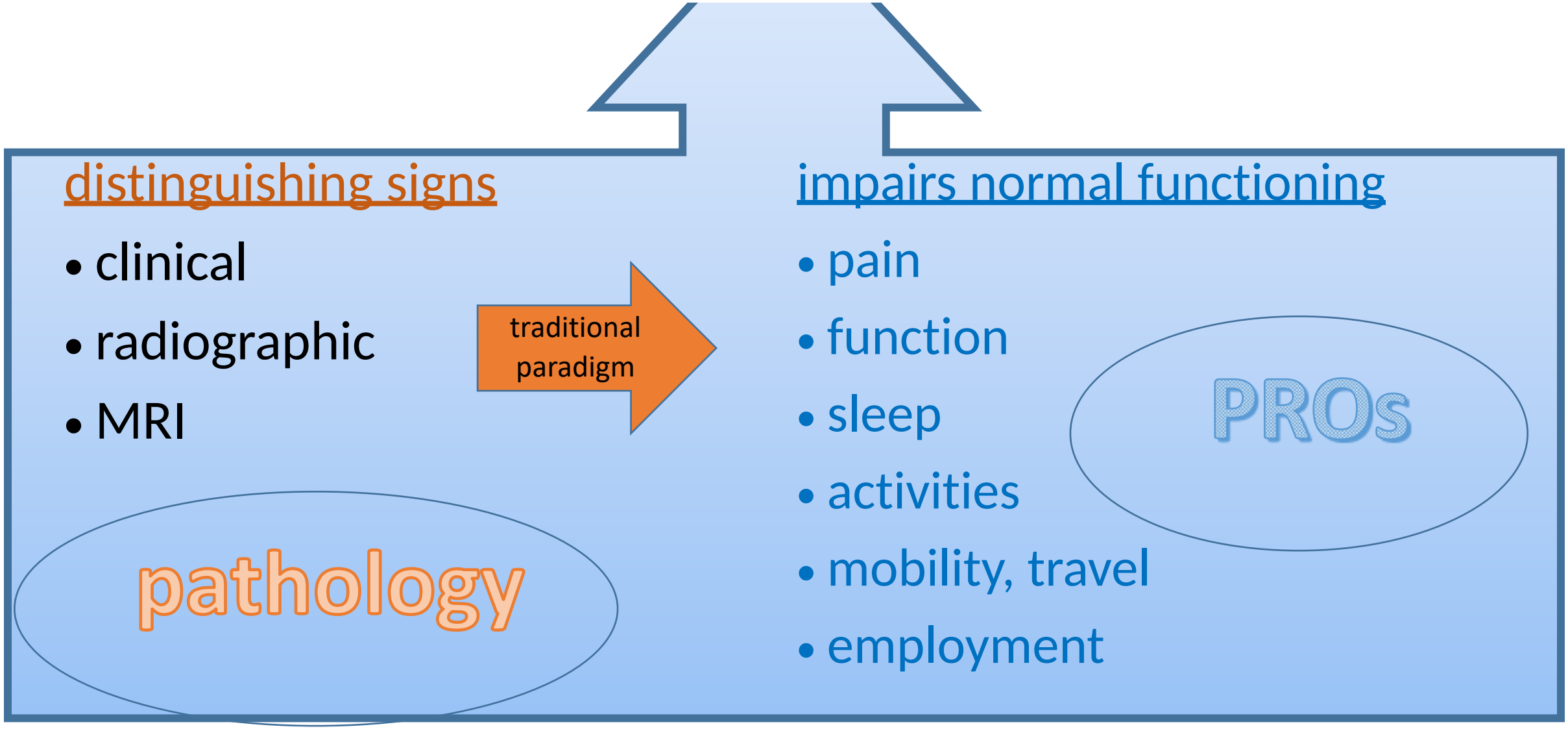
pathology

impairs normal functioning

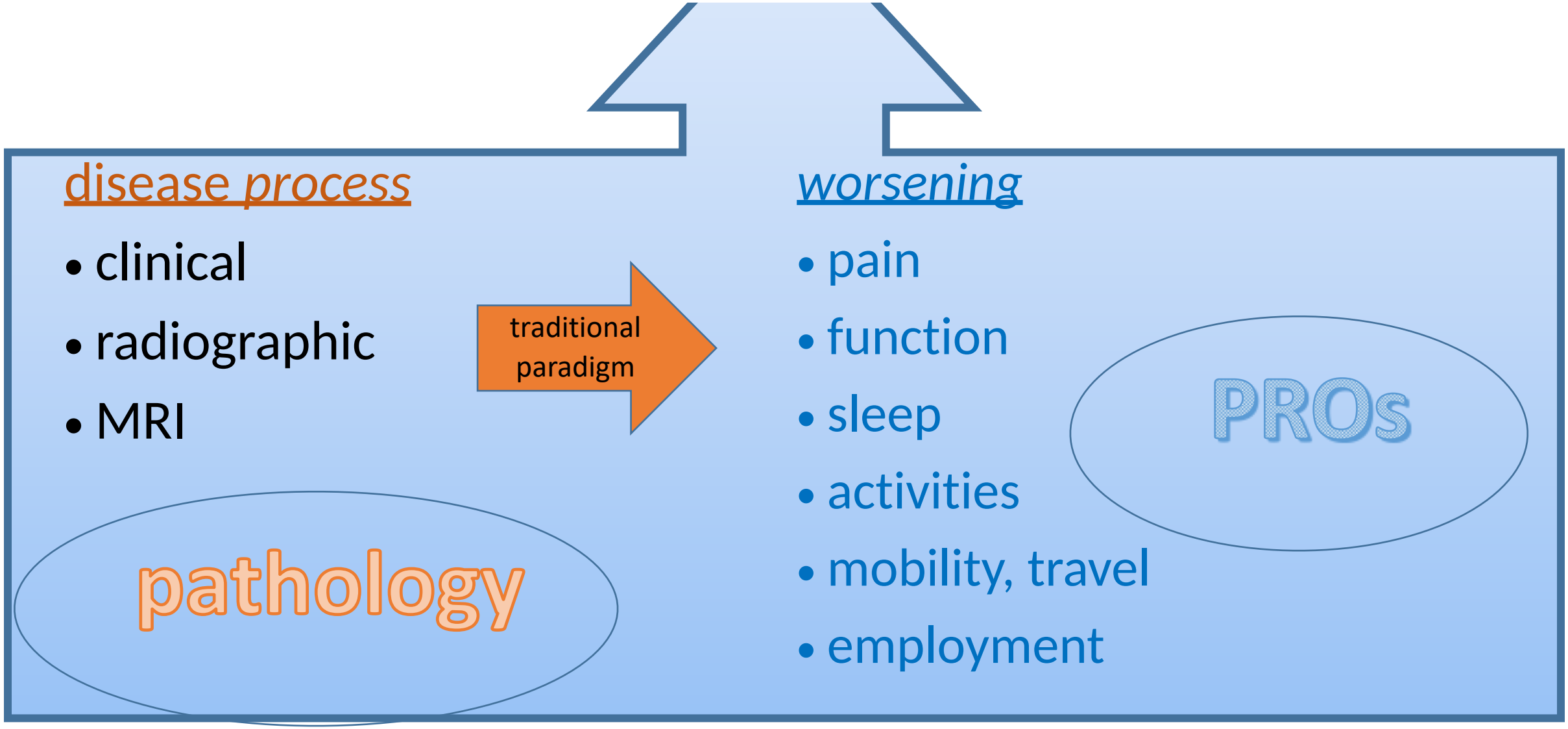
- pain
- function
- sleep
- activities
- mobility, travel
- employment

PROs

construct of disease severity



construct of disease ***progression***



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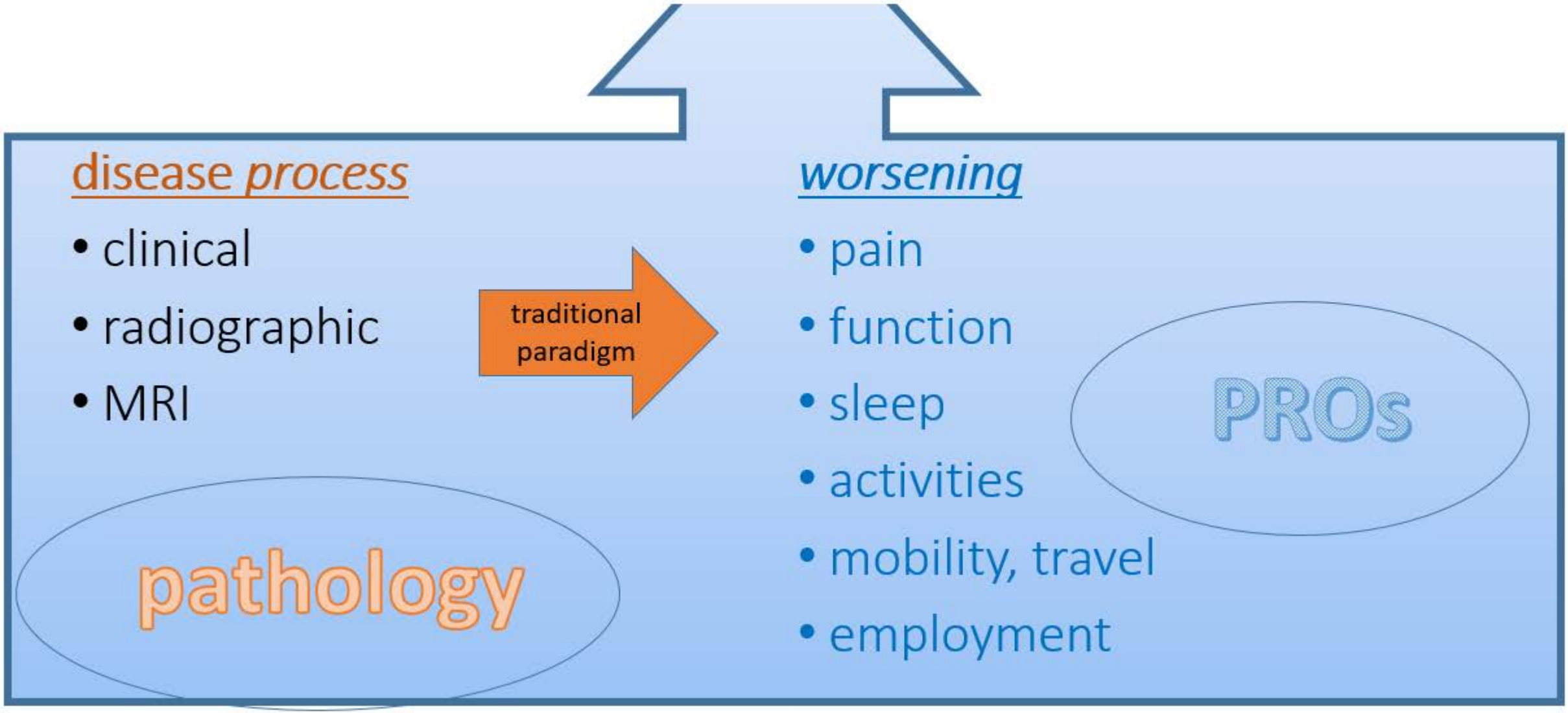
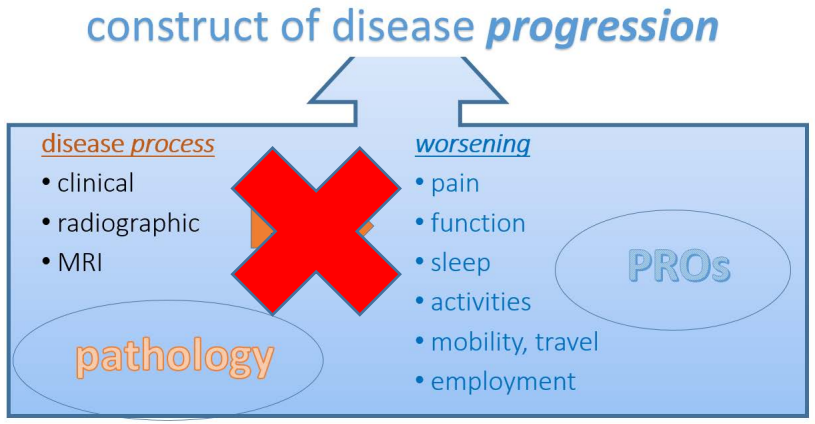
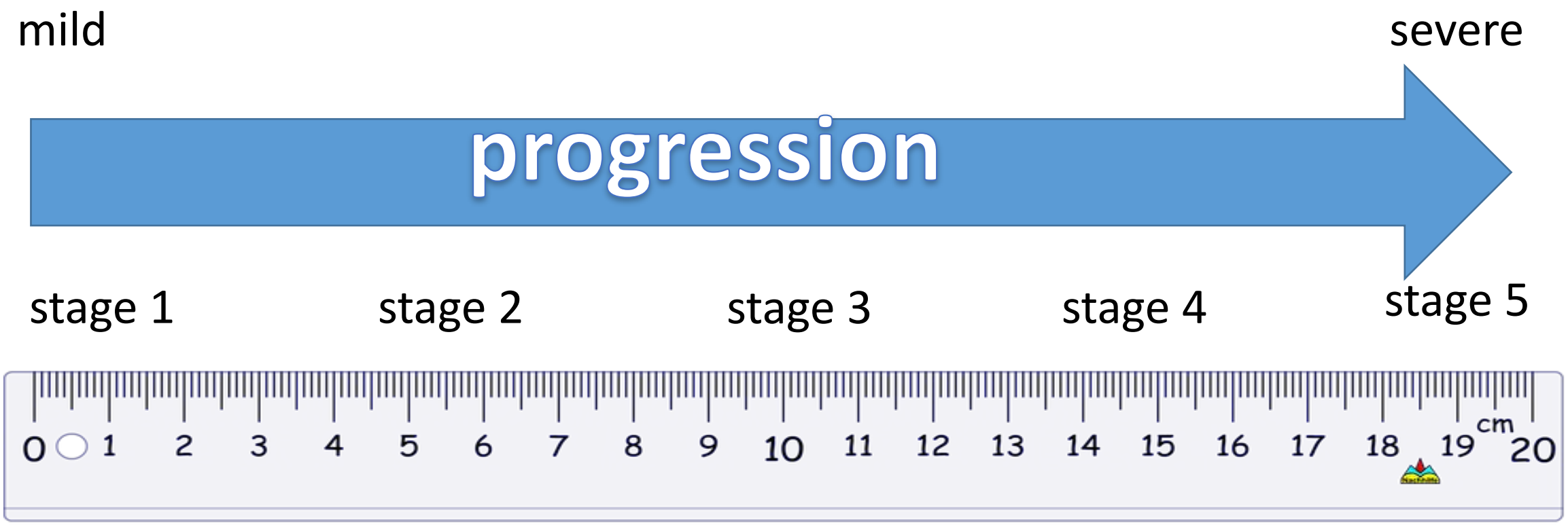


Problems with the model



1. No core / unifying measure of disease severity
   - No single (or composite) measure known reflect overall severity



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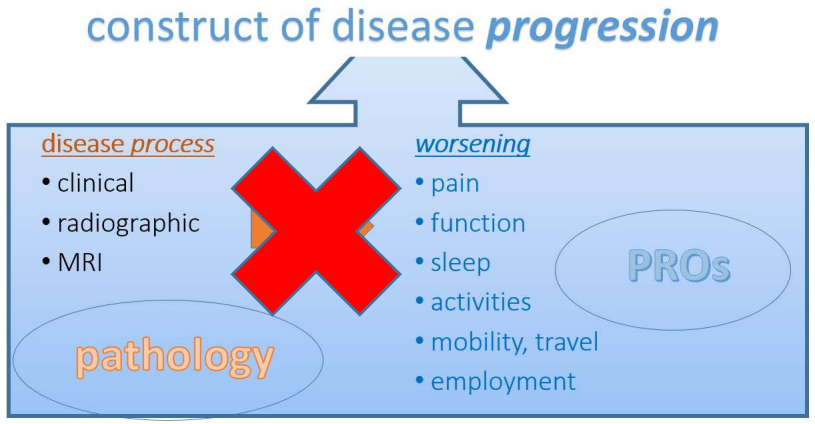


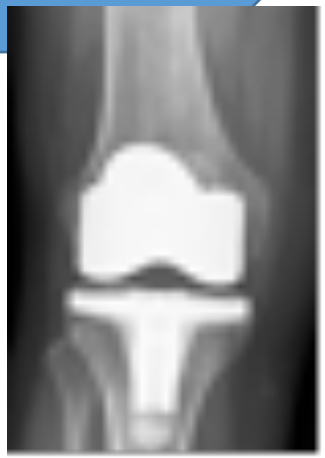
1. No core / unifying measure of disease severity

- TKA is appealing
  - integrates STRUCTURE and PROs
  - But is problematic*
  - Might be usable if incidence was higher

End of the road

progression

stage 1 stage 2 stage 3 stage 4



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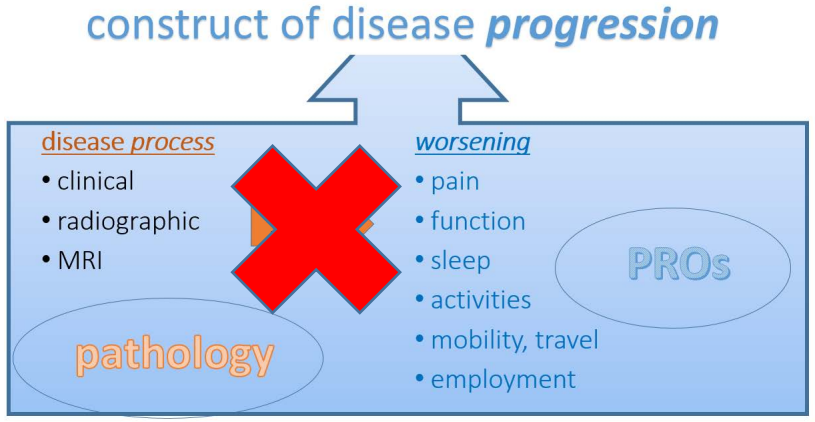

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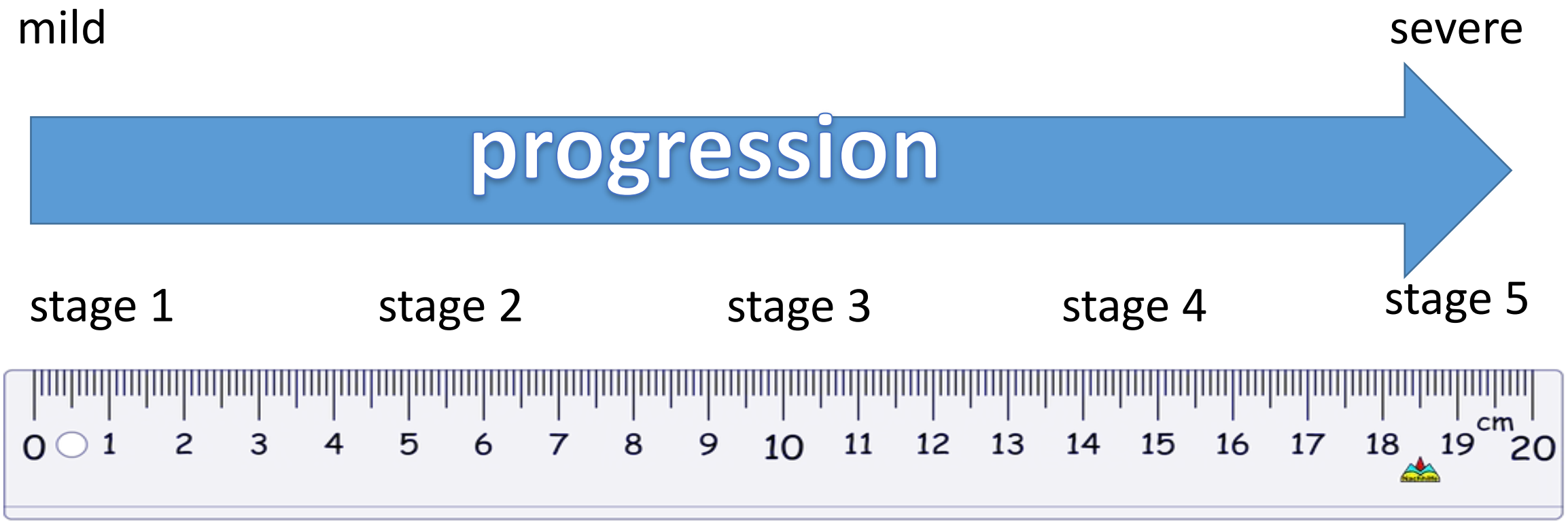

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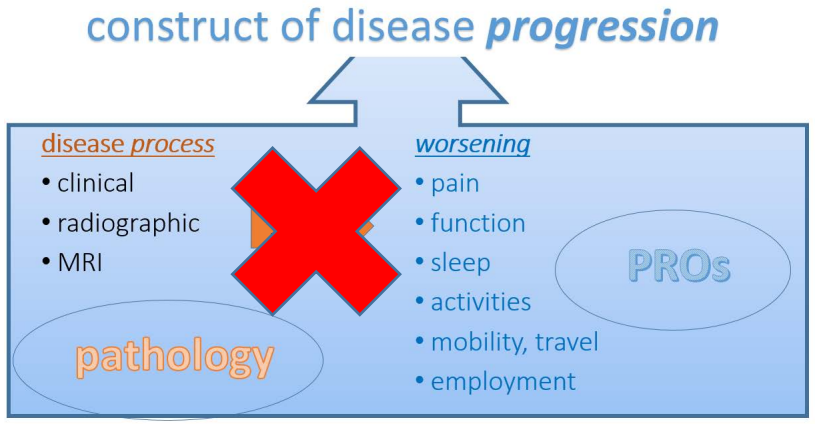

1. No core / unifying measure of disease severity
- No single (or composite) measure known reflect overall severity
- **Structure vs. PROs**
  - disease 'modification' requires **structure** + **PRO** effect
    - **Illogical on many levels**
      - PRO / function improvement should be the goal
      - Poorly related outcomes
        - What is the *disease*?
        - Requires TWO targets (empirical evidence supports this)
    - Contemporary structure measures mostly = accumulated changes
      - Proxy measures of structural severity (eg JSW) -> misconstrued targets (hyaline cartilage)
      - Not measures of *process*

Problems with

1. No core / unifying measur
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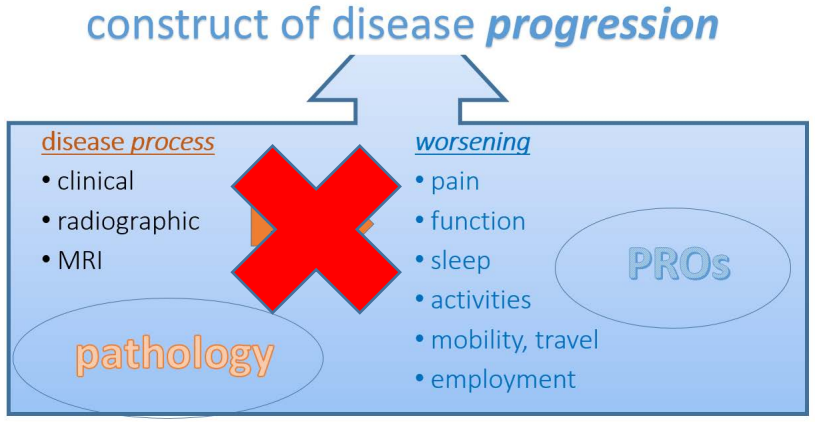


pports this)
ted changes
ued targets (hyaline cartilage)

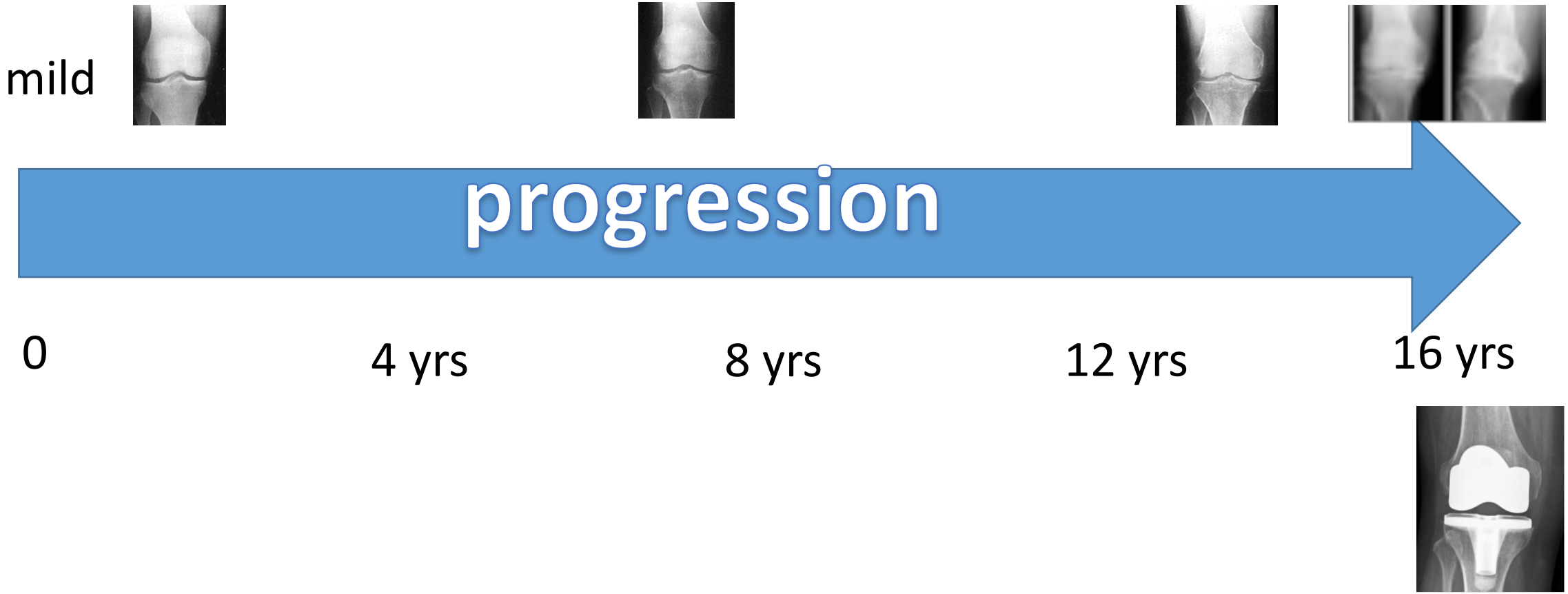
Transforming structural outcomes into process measurements

Measure change (= a proxy)

KL, JSW, cartilage volume…..

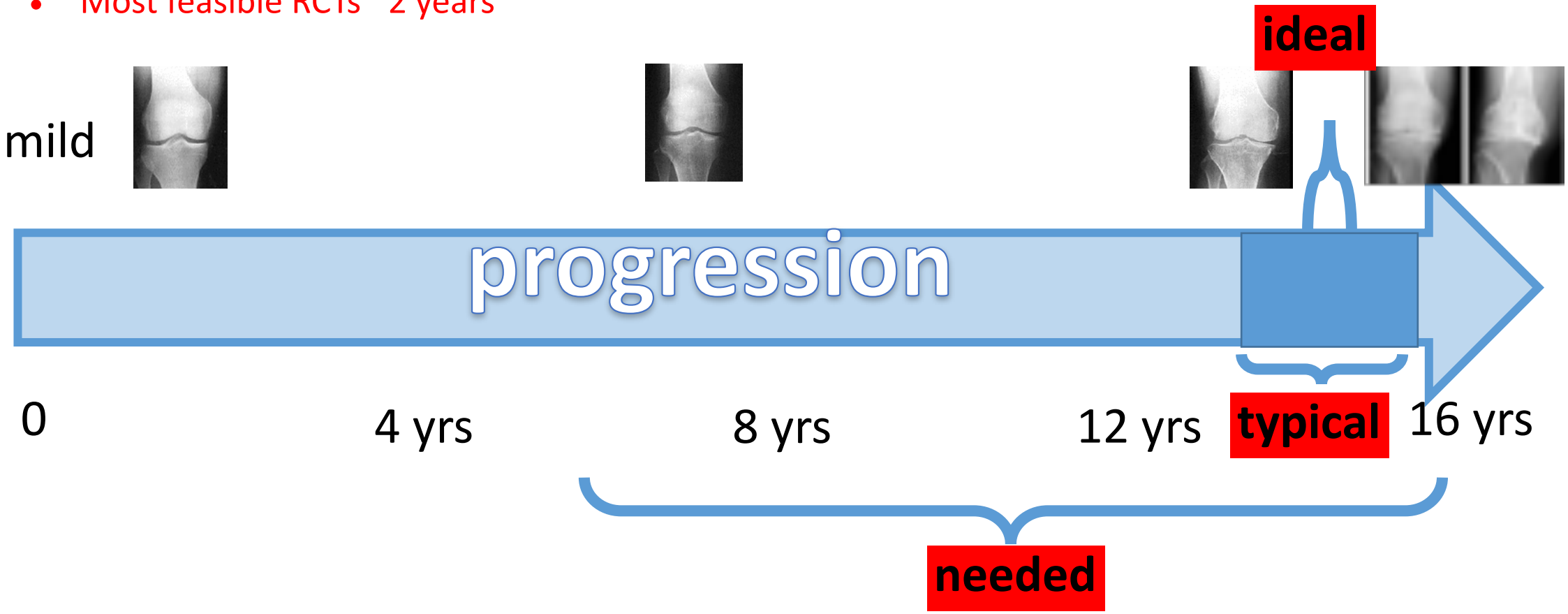
Barriers to measuring OA progression

1. Long timecourse…
2. Many do not progress



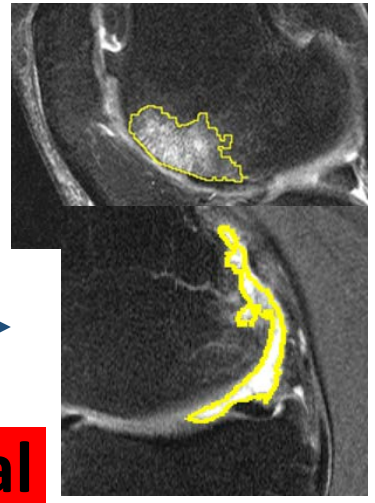
Barriers to measuring OA progression

1. Long timecourse…
2. Many do not progress
   - Most feasible RCTs ~2 years



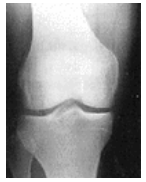
Barriers to measuring OA progression

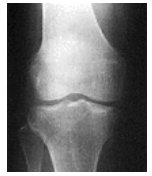
1. Predictive Biomarkers…
2. High sensitivity to change, discriminative, clinical validity
3. Technological barriers / solutions

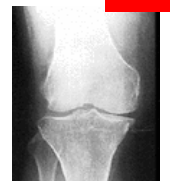


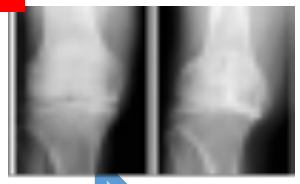
ideal

mild







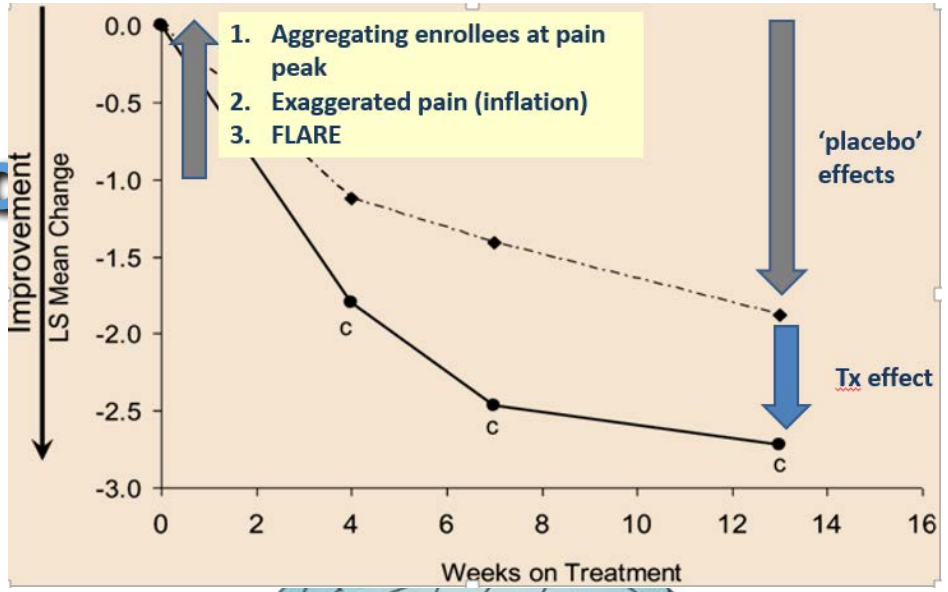


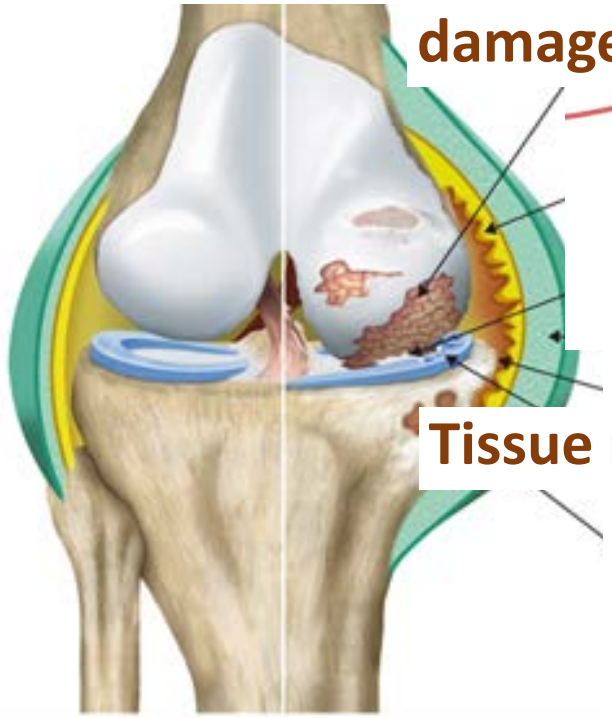
progression

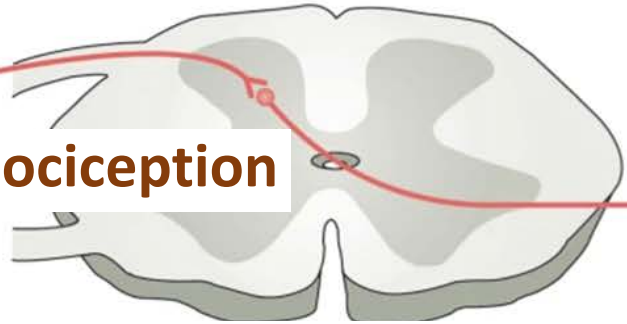
0 4 yrs 8 yrs 12 yrs 16 yrs

Barriers to measuring OA progressio

1. Measurement of PAIN
   - The brain is getting in the way
   - People have two knees (usually)







- Subjective, individual, contextualized
- Modulated in the NS and CNS
- nociception, sensitization, pain states
- Numerous measurement issues in RCTs

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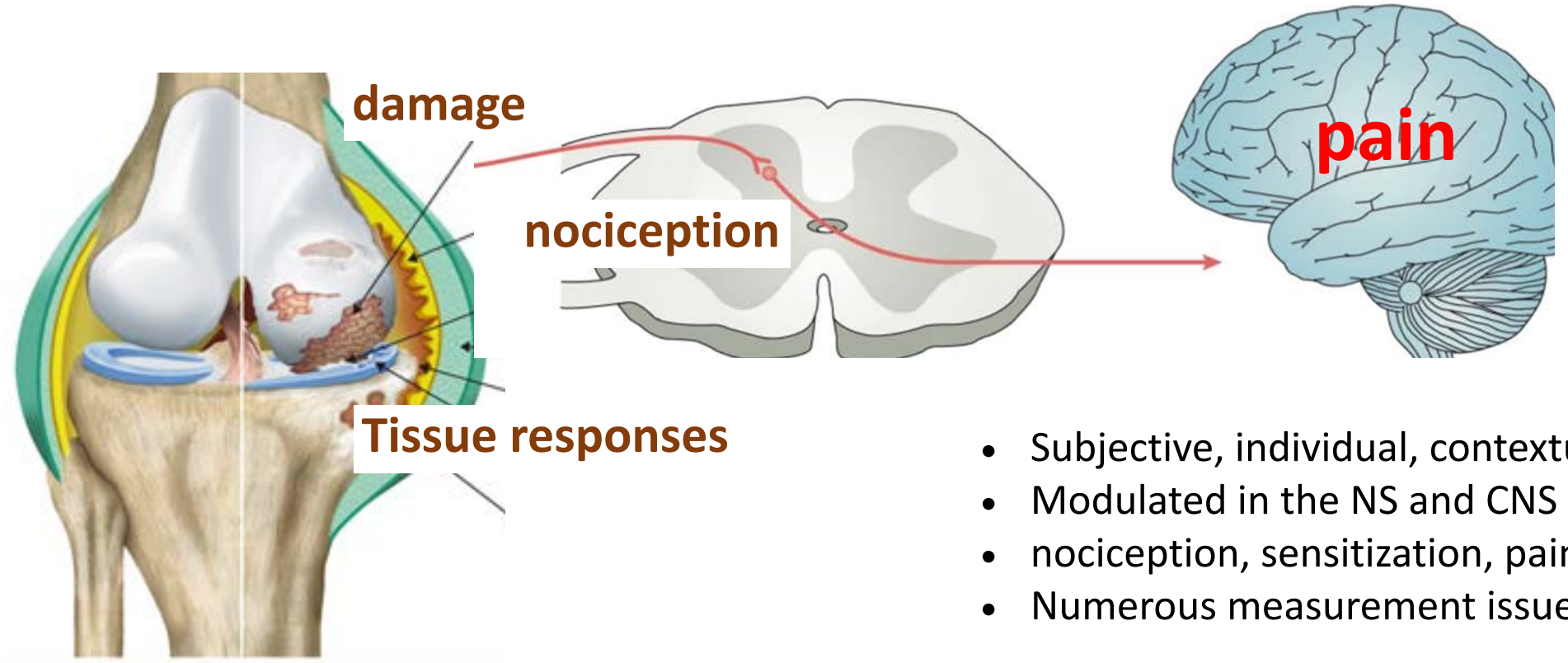

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Summary: Challenges with Assessment of Progression: Clinical and Structural

Cognitive inteference from outdated heuristics of OA (cartilage)

Absence of unified/core measurement of clinical severity

Lack of understanding of the structure / PRO relationship