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

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• 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

Osteoarthritis or Wear and Tear Arthritis
- 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

Kellgren & Lawrence grading system
OA development in late 20th / early 21st C

- Imaging
- Biopsies
- Clinical studies
- Epidemiology
- Biomechanical
Heuristic evolution of OA pathogenesis

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

**impairs normal functioning**
- pain
- function
- sleep
- activities
- mobility, travel
- employment

**pathology**

**PROs**

**traditional paradigm**
**construct of disease severity**

**distinguishing signs**
- clinical
- radiographic
- MRI

**impair normal functioning**
- pain
- function
- sleep
- activities
- mobility, travel
- employment

**pros**

**pathology**

**traditional paradigm**
construct of disease *progression*

**disease process**
- clinical
- radiographic
- MRI

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

**pathology**

**PROs**

traditional paradigm
The construct of disease progression involves:

**Disease Process**
- Clinical
- Radiographic
- MRI

**Worsening**
- Pain
- Function
- Sleep
- Activities
- Mobility, travel
- Employment

**PROs**

Traditional paradigm:

**Pathology**
Problems with the model

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

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

stage 1  stage 2  stage 3  stage 4
Problems with the model

1. No core / unifying measure of disease severity
   • No single (or composite) measure known reflect overall severity
   • Structure vs. PROs

mild

progression

severe

stage 1  stage 2  stage 3  stage 4  stage 5
Problems with the model

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 measure
   • No single (or composite)

2. Structure vs. PROs
   • disease ‘modification’
     • Illogical on many levels
     • PRO / function improvement
     • Poorly related
     • What is the disease?
     • Requires TWO targets (empirical evidence supports this)

3. Contemporary structure measures
   • Proxy measures
   • Not measured

4. Proxy measures of severity (e.g., JSW)
   • Misconstrued 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

mild

progression

0  4 yrs  8 yrs  12 yrs  16 yrs
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

mild

progression

ideal

0  4 yrs  8 yrs  12 yrs  16 yrs
Barriers to measuring OA progression

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
Barriers to measuring OA progression

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Summary: Challenges with Assessment of Progression: Clinical and Structural

Cognitive interference from outdated heuristics of OA (cartilage)
Absence of unified/core measurement of clinical severity
Lack of understanding of the structure / PRO relationship