OARSI Initiative to Develop Classification Criteria for Symptomatic Knee OA at an Early Structural Stage (EsSKOA)

The FACTs

(January 2026)

Goal of the Initiative

To expand the construct of symptomatic knee OA to include those earlier in the course of disease who have not yet developed established radiographic structural abnormalities

To do so, we are developing classification criteria for Symptomatic Knee OA at an Early Structural Stage (EsSKOA)

The criteria need to identify ‘early-stage’ knee OA cases & exclude mimickers with high specificity

Rationale

In the early stages of OA, people may have knee symptoms with little or no OA structural abnormalities on radiographs

People with symptoms deserve symptomatic treatment irrespective of whether they progress radiographically

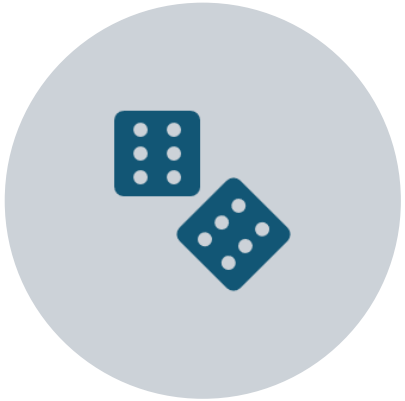
People with symptoms who are at high risk of radiographic progression deserve care that may reduce this risk

Enrollment of people with symptomatic knee OA earlier in the disease course into DMOAD clinical trials may enhance the likelihood of trial success.

Well-established precedents in other diseases

- New classification criteria in other diseases expanded construct to earlier stages of disease:
  - Rheumatoid arthritis
  - Non-radiographic axial spondyloarthritis (ankylosing spondylitis)

This effort ***is not*** about pre-clinical OA



By pre-clinical, we mean '*pre-symptoms*'.

Regulatory approval of disease-modifying therapies requires evidence of improvement in *patient-relevant outcomes.*

Thus, the effort to develop classification criteria currently focuses on those *with symptoms* rather than asymptomatic pre-clinical OA.

Once the EsSKOA criteria are developed & validated, studies can…

- Identify risk factors for “progression” (symptomatic, structural or other biomarkers) in people with EsSKOA
- Identify risk factors for development of “incident EsSKOA”

Future Clinical Trials in KOA

- Assuming regulatory approval of EsSKOA as an indication, trial inclusion would be based on EsSKOA + *additional criteria*, as for any clinical trial
- For example:
    - DMOAD trial: EsSKOA with risk factors for progression (TBD) or a specific mechanistic phenotype, e.g., certain clinical characteristics or endotype
    - Symptom treatment trial: EsSKOA with a threshold level of symptom severity

What is our methodological approach?

We're following the ACR–EULAR framework for classification criteria development

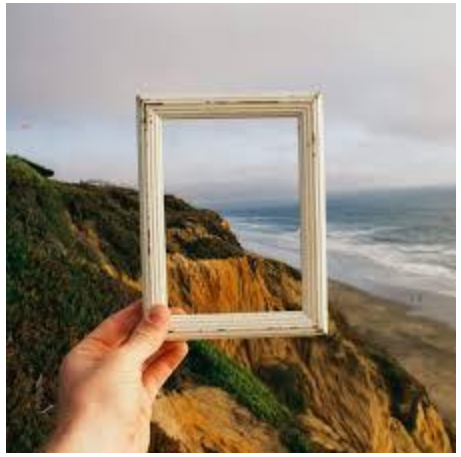
The goal is to find the most concise combination of factors that, when applied to individuals with undiagnosed knee symptoms, can accurately identify those with EsSKOA

Phase 1	Phase 2	Phase 3	Phase 4
• Generation of a list of **candidate items** that should be considered in criteria development	• Data collection & analysis to examine the ability of the candidate items, individually and in combination, to discriminate people with EsSKOA from other causes of knee symptoms (mimics) and from individuals with established knee OA	• Informed by the evidence, a consensus-based decision analysis process to identify those factors (& their relative weights) that influence the probability that the individual has EsSKOA	• Criteria refinement and validation

What have we done thus far?

January 2026

Phase 1 – Framing the Work



Thinking about the target population in which the criteria might be applied*

- Adults (18+) ***with*** knee symptoms (pain, aching, stiffness, discomfort) ***but not with***…
  - Established KOA in tibiofemoral OR patellofemoral joints on weight-bearing fixed flexion OR skyline knee radiographs
  - Previous joint replacement or osteotomy
  - Acute injury requiring medical care or knee surgery in past 6 months
  - Another condition more likely to explain the knee symptoms, e.g., pre-existing inflammatory arthritis

***The target population will be finalized in Phase 3.**

Justification for exclusions

Prior surgery or an "acute knee injury":	• Would not be enrolled in a clinical trial of a DMOAD therapy
Another condition more likely to explain symptoms:	• While people may have more than one condition (e.g., OA with gout / RA), these individuals would not generally be entered into clinical trials as it would be difficult to interpret response to therapy
Established radiographic OA:	• Already included in trials

How will we define structural stage?

We refer to radiographic stage to define structure.

Radiography is simple, widely accepted, and available in most countries.

Radiography has many limitations, but it is still a proxy for structural OA stage.

MRI?

- To be feasible for use in all settings, the classification criteria should not rely on tests that are not readily available everywhere, e.g., advanced imaging, non-commercial biomarkers
- If MRI features prove discriminatory for EsSKOA, they may be incorporated as **optional criteria**

Phase 1 – Elaboration of Candidate Items

- Multiple strategies were used to identify POTENTIAL candidate items for consideration in criteria development to differentiate EsSKOA from other conditions that cause knee symptoms (“mimics”)
- **86 candidate items** being considered:
  - **Patient history**
  - **Knee symptoms**
  - **Knee examination**
  - **Knee radiographs**
  - **Knee MRI**
  - **Laboratory tests** (RF, anti-CCP, urate, others)

King et al, 2025

Phase 1: What are the mimic conditions?

- Based on Expert Clinician Delphi Survey, most common mimics are:
  - Traumatic collateral ligament strain
  - Patellofemoral pain syndrome
  - Patellar tendonitis
  - Meniscal tear
  - Bursitis
  - Undiagnosed immune-mediated inflammatory arthritis
  - Undiagnosed crystal-induced inflammatory arthritis
  - Baker’s cyst

Hawker et al, 2025

Phase 2: Candidate Item Analyses

Candidate item analysis

- Requires data (information) about the candidate items on large numbers of people/knees
- An environmental scan for existing datasets identified 19 cohorts
  - A review of the eligibility criteria and variables available determined that there is unlikely to be sufficient data available for candidate items AND on individuals without established radiographic knee OA or mimic conditions
  - A pilot study is being developed to test this assumption in the NIH-funded OsteoArthritis Initiative, OAI, dataset

Primary Data Collection of Candidate Items in Symptomatic Knees

Adults with 1-2 eligible knees

Eligible knees:

- Symptoms at any time in the past 3 months
- No surgery/injury in the past 6 months
- No joint replacement ever
- No other established diagnosis, e.g., dx RA

We will recruit ~ 200 each with EsSKOA, a mimic condition or established radiographic knee OA (rKOA)

Recruitment status based on expert clinician assessment and radiographs (KL 2+)

Assessments:

Standardized patient questionnaire

Standardized expert clinician physical examination

Laboratory testing

Radiographs – TF/PF

MRI – those without KL 2+ on radiographs

Additional biospecimens will be collected to enable future consideration of novel biomarkers in EsSKOA classification

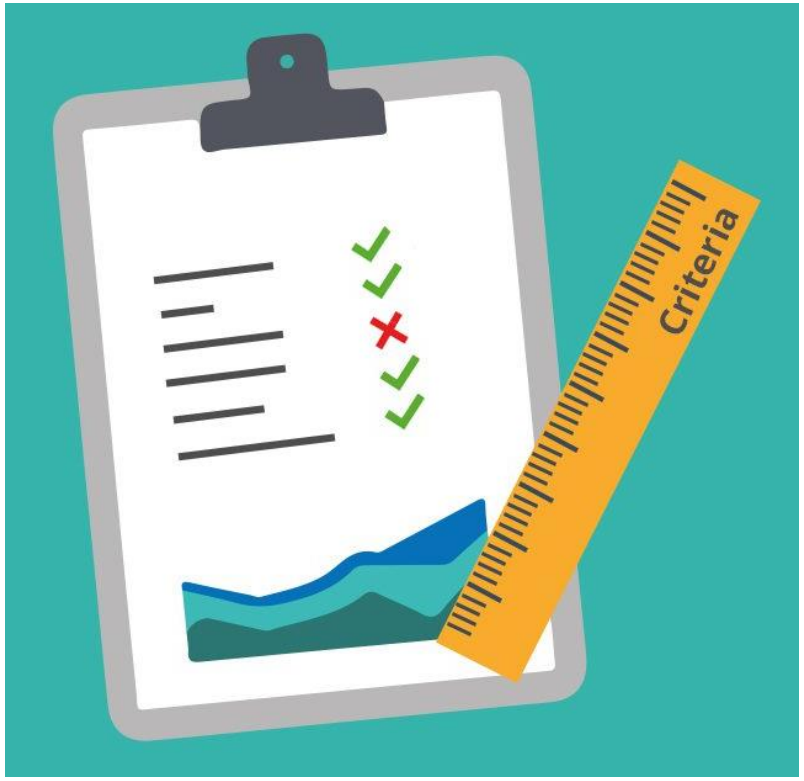
Blinded adjudication process to assign 'gold standard case status' (EsSKOA or mimic condition)

Analyses will assess the association of candidate items (independent variables) to case status (EsSKOA – yes/no)

Recruitment of Expert Clinicians
(to serve as Phase 2 Adjudicators & Phase 3 Expert Panel Members)

Adjudicators & expert panel members must represent a breadth of clinical expertise in “knee” diagnoses	The differential diagnosis for symptomatic knees is broad & discernment of the most likely cause of the symptoms challenging	OARSI is an international community that values inclusion & diversity
We will recruit approximately equal numbers of rheumatologists, physiotherapists, sports medicine / primary care physicians, and orthopaedic surgeons.	We will recruit individuals with at least 10 years’ clinical experience who have seen ≥ 5 patients per month, on average, presenting with undiagnosed knee symptoms.	We will recruit individuals to ensure broad geographic representation (continents) and both men and women.

Phase 3: Criteria Development



Criteria Development

- Assemble the Expert Clinical Panel
  - 16-20 clinical experts from the four clinical disciplines, with representation across continents & men and women
- Expert Panel activities pre-meeting
  - Review Phase 2 candidate item analysis findings
  - Review a spectrum of “paper” cases representing people presenting with undiagnosed knee symptoms & assign a most likely diagnosis (from very likely EsSKOA to very likely a mimic condition)

Expert Panel Meeting

1. Discussion of cases for which there was lack of consensus on EsSKOA vs a mimic condition
   - What features were important in ruling in / ruling out EsSKOA?
   - Identifies the domains / categories within domains for the classification criteria
2. Discrete choice experiment using 1000 Minds® software
   - Derives the weights for domains/ categories within domains (sum of the weights is the estimated probability that a patient has EsSKOA)
   - Determine threshold 'score' to optimize specificity for identifying EsSKOA & excluding mimics
3. Finalize 'target population' for application of the criteria

Phase 4: Criteria validation

Criteria validation

We will recruit an additional 200 participants in Phase 2 to serve as the independent ‘validation’ sample

In those subjects, we will calculate the sensitivity, specificity, and predictive values for discriminating people with EsSKOA from those with mimic conditions

Revisions may be required, e.g., shift in score threshold for classification, based on results

References

- Mahmoudian A, King LK, Liew JW, Wang Q, Berenbaum F, Das S, Ding C, Emery CA, Filbay SR, Hochberg MC, Ishijima M, Kloppenburg M, Lane NE, Losina E, Mobasheri A, Appleton CT, Englund M, Lohmander LS, Runhaar J, Turkiewicz A, Hawker GA, Neogi T, Haugen IK; OARSI Early-stage Symptomatic Knee Osteoarthritis Initiative. Reframing Early-stage Symptomatic Knee Osteoarthritis (EsSKOA): A Strategic Lens for Trial Design. Osteoarthritis Cartilage. 2025 Dec 20:S1063-4584(25)01279-8. doi: 10.1016/j.joca.2025.12.016.

- King LK, Mahmoudian A, Liew JW, Wang Q, Stanaitis I, Schiphof D, Callahan LF, Hunter DJ, Appleton CT, Turkiewicz A, Englund M, Lohmander LS, Haugen IK, Hawker GA, Neogi T, Runhaar J; OARSI Early-stage Symptomatic Knee Osteoarthritis Initiative. Elucidating the initial symptoms and experiences of knee osteoarthritis: An international patient survey. Osteoarthritis Cartilage. 2025;33(9):1147-1152. doi: 10.1016/j.joca.2025.05.008.

- Hawker GA, King LK, Liew JW, Wang Q, Mahmoudian A, Jansen NEJ, Stanaitis I, Berenbaum F, Das S, Ding C, Emery CA, Filbay SR, Hochberg MC, Ishijima M, Kloppenburg M, Lane NE, Losina E, Mobasheri A, Runhaar J, Appleton CT, Turkiewicz A, Englund M, Lohmander LS, Haugen IK, Neogi T; OARSI Early-stage Symptomatic Knee Osteoarthritis Initiative. OARSI initiative to develop classification criteria for early-stage symptomatic knee OA (EsSKOA): What conditions should be considered in the differential diagnosis of EsSKOA? Osteoarthritis Cartilage. 2025;33(9):1141-1146. doi: 10.1016/j.joca.2025.05.005.

- King LK, Liew JW, Mahmoudian A, Wang Q, Jansen NEJ, Stanaitis I, Hung V, Berenbaum F, Das S, Ding C, Emery CA, Filbay SR, Hochberg MC, Ishijima M, Kloppenburg M, Lane NE, Losina E, Mobasheri A, Turkiewicz A, Runhaar J, Haugen IK, Appleton CT, Lohmander LS, Englund M, Neogi T, Hawker GA; OARSI Early-stage Symptomatic Knee Osteoarthritis Initiative. Multi-centre modified Delphi exercise to identify candidate items for classifying early-stage symptomatic knee osteoarthritis. Osteoarthritis Cartilage. 2025;33(1):155-165. doi: 10.1016/j.joca.2024.10.016.
  - Corrigendum to "Multi-centre modified Delphi exercise to identify candidate items for classifying early-stage symptomatic knee osteoarthritis". Osteoarthritis Cartilage. 33(4):530-533. doi: 10.1016/j.joca.2025.01.002. Erratum for: Osteoarthritis Cartilage. 2025;33(1):155-165. doi: 10.1016/j.joca.2024.10.016.

- Mahmoudian A, King LK, Liew JW, Wang Q, Appleton CT, Englund M, Haugen IK, Lohmander LS, Runhaar J, Turkiewicz A, Neogi T, Hawker GA; OARSI Early-stage Symptomatic Knee Osteoarthritis Initiative. Timing is everything: Towards classification criteria for early-stage symptomatic knee osteoarthritis. Osteoarthritis Cartilage. 2024;32(6):649-653. doi: 10.1016/j.joca.2024.02.888.

- King LK, Mahmoudian A, Waugh EJ, Stanaitis I, Gomes M, Hung V, MacKay C, Liew JW, Wang Q, Turkiewicz A, Haugen IK, Appleton CT, Lohmander S, Englund M, Runhaar J, Neogi T, Hawker GA; OARSI Early-stage Symptomatic Knee Osteoarthritis Initiative. "You don't put it down to arthritis": A qualitative study of the first symptoms recalled by individuals with knee osteoarthritis. Osteoarthr Cartil Open. 2023;6(1):100428. doi: 10.1016/j.ocarto.2023.100428.

- Liew JW, King LK, Mahmoudian A, Wang Q, Atkinson HF, Flynn DB, Appleton CT, Englund M, Haugen IK, Lohmander LS, Runhaar J, Neogi T, Hawker G; OARSI Early Osteoarthritis Classification Criteria Task Force. A scoping review of how early-stage knee osteoarthritis has been defined. Osteoarthritis Cartilage. 2023;31(9):1234-1241. doi: 10.1016/j.joca.2023.04.015.

- Hawker GA, Lohmander LS. What an earlier recognition of osteoarthritis can do for OA prevention. Osteoarthritis Cartilage 2021;29:1632-1634. doi: 10.1016/j.joca.2021.08.007.

Who is leading this initiative?

Advisory Committee

Stefan Lohmander (Chair)

Francis Berenbaum, Marc Hochberg, Muneaki Ishijima, Nancy Lane, Margreet Kloppenburg, Siddharth Das, Ali Mobasheri, Elena Losina, Changhai Ding, Carolyn Emery, Stephanie Filbay

Steering Committee

Ida Haugen (Chair)

Martin Englund, Gillian Hawker, Tuhina Neogi, Stefan Lohmander, Armaghan Mahmoudian, Tom Appleton, Jos Runhaar

Methodology Working Group

Gillian Hawker and Tuhina Neogi (Co-chairs)

Aleksandra Turkiewicz, Martin Englund, Jos Runhaar, Armaghan Mahmoudian, Lauren King, Jean Liew, Qiuke Wang

- Expert Clinical Panel (TBD)
- Patient Research Partners (appointed)
- Case Status Adjudicators (TBD)

Ad hoc topic expertise

- Statistics
- Biomarkers
- Imaging
- Clinical trials

Project Manager:
Arin Deveci

Funding received to date for this initiative

Got questions?

Please contact our Project Coordinator
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