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Novel Framework for Measuring Whole Knee Osteoarthritis Progression Using Magnetic Resonance Imaging

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Abstract

Objective: We developed and validated a set of composite scores that combine quantitative magnetic resonance (MR)-based measurements of hyaline cartilage damage, bone marrow lesions (BMLs), and effusion-synovitis into composite scores.

Methods: We selected 300 participants (development cohort=100, validation cohort=200) from the Osteoarthritis Initiative with complete clinical, radiographic, and MR data at baseline and 24 months. We used semi-automated programs to quantify tibiofemoral and patellar cartilage damage, BML volume, and whole-knee effusion-synovitis volume. The candidate composite scores were formed by summing changes from baseline to 24 months based on pre-specified methods. We evaluated the candidate composite scores 1) ability to differentiate groups with and without KOA progression (17 radiographic and patient-reported definitions), 2) sensitivity to change (standardized response means), and 3) relative performance relating to legacy outcome measures of KOA progression.

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Results: Three out of 13 developed composite scores qualified for testing in the validation cohort (ranked by sensitivity to change): 1) whole-knee cumulative cartilage damage, 2) unweighted total knee score, and 3) BML+effusion-synovitis volume. Change in cumulative cartilage damage associated with radiographic progression (Kellgren-Lawrence: OR=1.84; Joint Space Width Progression: OR=2.11). Changes in the unweighted total knee score (OR=1.97) and BML+effusion-synovitis score (OR=1.92) associated with WOMAC knee pain progression

Conclusion: Two composite scores emerged, reflecting discrete domains of KOA progression. First, cumulative damage, which is measured by a whole-knee cartilage damage score, reflects the damage accrued over time. Second, dynamic disease activity, which is measured by a BML+effusion-synovitis score, relates with changes in a patient's state of disease and symptoms.

Keywords

Magnetic Resonance Imaging (MRI); Osteoarthritis; Cartilage; Disease Activity; Synovitis

Optional Terms:

Knee; Bone Marrow Lesions; Effusion

Osteoarthritis of the knee (KOA) is a highly prevalent age-related disorder and a leading cause of pain and functional impairment in the population(1). Despite this, there are few effective interventions for KOA and none accepted to reduce its structural progression(2). One of the most significant obstacles to testing and developing disease-modifying therapies for KOA is the absence of measures of disease progression that meaningfully reflect a change in patient status(3). For regulatory agencies to accept an imaging biomarker of KOA progression the biomarker must: 1) reflect the complex pathology throughout the joint, 2) address the apparent discordance between structural changes and signs/symptoms/function, 3) offer a standardized definition of disease progression, and 4) reliably predict meaningful changes in symptoms and function(3).

Semiquantitative scales are comprehensive, but the approach is inherently insensitive to change(4) and limited by the absence of a validated composite measurement reflecting severity in the whole knee(5, 6). Quantitative measurements in knees have also been limited by a focus on single structures (e.g., hyaline cartilage).

Over the past decade, there has been a paradigm shift from conceptualizing KOA as a single-structure disorder, based in hyaline cartilage, to a multi-tissue 'whole-organ' failure of diarthrodial joints(2). MR imaging has revealed structural features, such as BMLs and effusion-synovitis, which are clinically relevant(12). BMLs reflect altered peri-articular bone morphology and density(13, 14) and associate with hyaline cartilage damage and pain(12, 15, 16). BMLs appear to be responsive to clinical intervention(17–19) and have been proposed as a therapeutic target for KOA disease modification(18, 20). Effusion-synovitis is also common in KOA and is strongly associated with pain(12, 21, 22) and hyaline cartilage loss(23, 24).

Combining these relevant features into a single quantitative composite knee score, rather than measuring each feature separately could advance the field towards by addressing 1) the multifactorial and complex etiopathogenesis of KOA, 2) the discordance between structural changes and signs/symptoms/function, and 3) the lack of consensus for the best definitions of disease progression. However, while this is an appealing concept, there are methodological issues that need to be addressed to determine if a composite score is practical, feasible, and valid. The first question is whether measures of each feature can be combined in a way that is internally (heuristically) consistent. For example, it is unclear if change in BMLs, which relates with change in pain, can or should be combined with change in hyaline cartilage, which relates to joint space narrowing. A second challenge is to determine how to mathematically combine the individual features into a single composite score that retains construct validity and optimizes the ability to detect a treatment difference (discriminative validity). Therefore, the goals of this study were to develop and validate candidate composite scores that combine quantitative measurements of hyaline cartilage damage, BMLs, and effusion/synovitis (Figure 1 and 2) into composite scores that are heuristically consistent; and then determine sensitivity to change, and identify the best performing composite scores in relation to established legacy measures of KOA progression (i.e., joint space with [JSW], Kellgren-Lawrence [KL] grade, WOMAC pain).

MATERIALS AND METHODS

Overview

To develop and validate composite, quantitative, MR-based outcome scores we selected 2 subcohorts from the Osteoarthritis Initiative (OAI), a multicenter cohort study of individuals with or at risk for symptomatic KOA in the United States. We used a *development* cohort (n=100) to develop and perform preliminary analyses to assess construct validity of candidate composite scores based on measures of radiographic progression as well as changes in quality of life and knee pain (Table 1). Then we used a *validation* cohort (n=200) to confirm the construct validity of the best-performing composite scores by determining which ones exhibit the best discriminative ability and sensitivity to change.

Selection of Subcohorts

The OAI included 4 clinical sites (Memorial Hospital of Rhode Island, The Ohio State University, the University of Maryland and Johns Hopkins University, and the University of Pittsburgh) and recruited between February 2004 and May 2006. Each clinical site and the coordinating center obtained institutional review board approval for the OAI. Informed consent was obtained from every participant.

In the course of prior analyses, the OAI investigators formed a Core Image Assessment sample that reflected people typically enrolled in clinical trials. This convenience sample consisted of one knee from 600 participants with symptomatic KOA at baseline (frequent knee pain and KL grade = 2 or 3) and complete baseline and 24-month data for clinical, radiographic, and MR outcomes(34). The current project used newer central radiographic readings, which explained why a few people had KL grade = 0, 1, or 4. We used the Core Image Assessment sample to assemble our 2 subcohorts for these analyses. We first

selected participants for the development cohort. Within each KL grade, we randomly sampled participants with and without radiographic progression (any increase in KL grade over 24 months). The process was then repeated for the validation cohort after excluding the participants in the development cohort.

Magnetic Resonance Images

Each OAI site acquired knee MR images at baseline and 24-month follow-up visits using identical Siemens 3.0 Tesla Trio MR systems and knee coils. The OAI used study-certified, licensed MR technologists and completed comprehensive quality control measurements to promote quality, provide consistency across sites, and longitudinal uniformity(25, 26).

Acquisitions included a 3-dimensional dual echo steady state (3D DESS) sequence (field of view=140mm, slice thickness=0.7mm, skip=0mm, flip angle=25 degrees, echo time=4.7ms, recovery time=16.3ms, 307×384 matrix, x-resolution=0.365mm, y-resolution=0.456mm) and an intermediate-weighted fat suppressed (IWFS) sequence (field of view=160mm, slice thickness=3mm, skip=0mm, flip angle=180 degrees, echo time=30ms, recovery time=3200ms, 313×448 matrix, x-resolution=0.357mm, y-resolution=0.511mm).

Radiographic Outcomes

OAI participants had annual bilateral weight-bearing, fixed-flexion posterior-anterior knee radiographs. Central readers provided KL grades, medial and lateral joint space narrowing (JSN) grades, and medial JSW measurements. The intra-rater agreement for KL and JSN grades using the weighted kappa ranged from 0.70 to 0.88 and the intraclass correlation coefficient (ICC) for JSW was >0.9(27). We used the baseline and 24-month data to define KL, JSN, and JSW progression. The operational definitions of progression in these constructs are in Table 1. Data are publicly available at <https://data-archive.nimh.nih.gov/oai> (kxr_sq_bu00 (version 0.8), kxr_sq_bu00 (version 3.7), kxr_qjsw_duryea00 (version 0.8), and kxr_qjsw_duryea03 (version 3.7)).

Patient-Centered Outcomes

The Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) questionnaire measuring knee-specific pain (0 to 20 scale) was obtained at each OAI visit. We used baseline and 24-month WOMAC pain scores to calculate pain progression. We used the 4 Knee Injury and Osteoarthritis Outcomes Scores (KOOS) quality of life questions because we were interested in the unique concepts they reflect: 1) awareness of knee problem, 2) modifying activities, 3) lack of confidence, and 4) difficulty with a knee. The operational definitions of progression in these constructs are in Table 1. Data are publicly available at <https://data-archive.nimh.nih.gov/oai> (allclinical00 (version 0.2.2) and allclinical03 (version 3.2.1)).

Quantitative Measurement of Change in Cartilage Damage

We used a validated approach(28–30) to quantify cartilage damage on the 3D DESS MR images from the baseline and 24-month visits (Figure 1). The Cartilage Damage Index (CDI) generates a single measure from measurements of cartilage thickness obtained from predetermined regions of interest distributed across 6 regions in the knee joint: medial

and lateral tibia, femur, and patella. We deployed a semi-automated interface to delineate the bone-cartilage boundary on the automatically selected MR images. We also used the interface to automatically identify the predefined informative locations to measure cartilage thickness in each of the 6 regions (9 locations in each tibiofemoral region, 12 locations in patellar regions). The CDI summary measure is calculated by summing the products of cartilage thickness, cartilage length, and voxel size from each of the informative locations. Intra-reader reliability (ICC) for the baseline measures 0.86 with >72 hours between read and re-read(28–32).

Quantitative Measurement of Change in Bone Marrow Lesion Volume

We measured BML volume in the medial and lateral tibia, femur, and patella regions using the IWFS MR sequence and a validated semi-automated software (Figure 2)(33). We defined BML as regions of high-signal intensity within a bone that appeared on >2 slices and were within 10mm of the articular surface(15, 34, 35). The software uses thresholding to delineate suspected BML regions. The reader (AC) manually adjusted the threshold and removed artifacts. All BML segmentation results were reviewed for quality by a second reader (JBD) and adjusted when necessary. Our reader had good intra-reader reliability among 20 knees measured twice with >48 hours between readings: ICC=0.98 for baseline BML volume.

Quantitative Measurement of Change in Effusion-Synovitis Volume

We measured whole knee effusion-synovitis volume using the IWFS MR sequence and a validated semi-automated software, using an approach that has been described previously (Figure 2)(36–38). Effusion-synovitis segmentation results were read by one reader (RS) and reviewed for quality by a second reader (MZ), with changes made when necessary. Our reader had good intra-reader reliability among 15 knees measured twice with >48 hours between readings: ICC=0.87 for baseline effusion-synovitis volume.

Analytic Approach

Standardizing MR-Based Measures of Change to the Same Scale—We generated 13 MR-based structural measurements: articular cartilage damage measured by CDI (6 measurements: medial and lateral femur, tibia, and patella), BML volume (6 measurements: medial and lateral femur, tibia, and patella), and effusion-synovitis volume (single whole-knee measurement). We adjusted each structural measure for knee size based on femur width (medial to lateral femoral epicondyle). Next, we subtracted the baseline mean and divided by the baseline standard deviation ($[\text{measure} - \text{baseline mean}] / \text{baseline standard deviation}$) to transform all measurements to the same scale (mean=0 and standard deviation=1). We calculated change in each structural measurement by subtracting the baseline from the 24-month value. We multiplied the CDI change measurements by (-1) to ensure greater change represented worsening disease burden among all the structural measurements.

Development of Candidate Composite Knee Scores—In the development cohort, we implemented 4 approaches to select features to combine into 13 candidate composite knee scores.

For the first approach, we created whole-knee composite scores, which included all 13 measures of change in cartilage, BML, and effusion-synovitis. We used 3 mathematical methods to calculate total MR-based scores: (1) unweighted summation, (2) inverse variance weighting, and (3) weighting according to the eigenvectors from a principal component analysis (PCA).

For the second approach, we used expert judgment based on the existing literature to select MR-based features that might reasonably be combined: (1) a cumulative cartilage damage score comprising all 6 measures of cartilage change and (2) a BML+effusion-synovitis composite using all 7 measures of change in BML and effusion-synovitis volumes. We used an unweighted sum (simple addition) to calculate these 2 candidate composite scores.

For the third approach, we used a data-driven approach based on a PCA to identify principal components (i.e., structural measures that cluster together based on correlated measures of change in MR-based features). The PCA enabled us to determine if structural measures group based on anatomic location (e.g., medial femoral BML volume and cartilage change) or within a given tissue (e.g., all BML volumes). Each principal component with an Eigenvalue >1 was considered a candidate composite knee score. For each component with Eigenvalue >1 , we calculated a candidate composite knee score by multiplying standardized measures of each MR-based feature that had a factor loading >0.4 (absolute value) in a principal component by its eigenvector divided by the sum of the eigenvectors of the contributory components.

For the fourth approach, we calculated 2 variables using an unweighted sum of BML or effusion-synovitis volumes in the whole knee.

Preliminary Evaluation of the Candidate Composite Scores in the Development Cohort.

To prune the set of candidate composite scores before advancing these to the validation sample, we performed preliminary analyses in the development cohort. We evaluated the performance of each candidate composite score to differentiate KOA progressors from nonprogressors based on 2-year change in 17 dichotomous measures of pain, quality of life, and radiography (Table 1) using Wilcoxon Rank Sum tests.

Our decision rule to identify the best-performing composite scores that warranted further validation was that a candidate composite score needed to differentiate (Wilcoxon Rank Sum p -value $<0.20(39)$) between groups with and without KOA progression for at least one measure in each of the 3 constructs: 5 measures of radiographic progression, 8 measures of quality of life, and 4 measures of knee pain (Table 1).

Confirmation of Validity of the Best-Performing Composite Scores.

In the validation cohort, we examined the best performing candidate composite scores from the development cohort. Specifically, we re-assessed their performance based on 3 criteria: 1) an ability to differentiate groups with and without KOA progression (radiographic and patient-reported), 2) sensitivity to change, and 3) associations with several commonly used outcome measures of KOA progression. First, to confirm whether a candidate quantitative composite knee score differentiated groups we evaluated the same 17 dichotomized

measures tested in the development cohort (requiring a Wilcoxon Rank sum p-value<0.05). Second, we calculated sensitivity to change for each candidate composite knee score using a standardized response mean (SRM) and interquartile range (IQR). Finally, we compared the performance of each candidate composite score using the area under the receiver-operating characteristics curve (AUC) and odds ratios (OR) in relation to commonly used outcome measures of KOA progression: change in KL Grade, JSW, and pain. To help compare our results with a prior biomarker study we adjusted for the same variables they selected: sex, race, age, body mass index (BMI), KL grade, WOMAC pain measure, use of pain medications, and minimum joint space width(40). The ORs and 95% confidence intervals were calculated using one standard deviation as the unit of analysis.

The assumption of linearity of the candidate composite scores with the outcomes was assessed. We used model diagnostics to identify potential outliers and influential points in the multivariable models. P-values were not adjusted to account for multiple comparisons. We performed all analyses using SAS 9.4 (Cary, NC).

RESULTS

We removed one participant from the development cohort and 3 participants from the validation cohort due to concerns with MR image quality (e.g., metal artifact, pathologic changes unrelated to KOA). The 99 participants in the development cohort had a mean age of 62 years, mean BMI of 30 kg/m², and 60% were female (Table 2). Similarly, the 197 participants in the validation cohort had a mean age of 61 years, mean BMI of 30 kg/m², and 54% were female (Table 2).

Development and Preliminary Evaluation of the Candidate Composite Scores in the Development Cohort.

The development process produced 13 candidate composite scores of structural changes (Table 3). Four of the 13 candidate composite scores met our decision rule based on discriminatory ability to advance as a best-performing composite score (Supplementary Table S1). These included (1) the unweighted total knee score (2) cumulative cartilage damage (3) BML+effusion-synovitis volume, and (4) change in the first principal component (patellar damage component).

Confirmation of Validity of the Best-Performing Composite Scores in the Validation Cohort.

Change in the BML+effusion-synovitis score was the only candidate composite knee score to differentiate progressors and nonprogressors for at least one measure within each of the 3 constructs (Supplementary Table S1). Specifically, change in the BML+effusion-synovitis score differentiated progressors and nonprogressors for 1 out of 5 radiographic measures, 1 out of 6 quality of life measures, and 3 out of 4 knee pain measures. Change in the cumulative cartilage damage differentiated groups for 4 radiographic measures, 1 quality of life measures, but none of the knee pain measures. Change in the unweighted total knee score differentiated groups for 3 radiographic measures, none of the quality of life measures, and 3 knee pain measures. Finally, change in the first principal component only

differentiated progressors and nonprogressors for one measure of radiographic progression. Hereafter, we omitted the first principal component from the analyses.

Sensitivity to Change in the Validation Cohort.

The cumulative cartilage damage had the greatest sensitivity to change (SRM=1.19; mean (SD)=0.88 (0.74)), followed by the unweighted total knee score (SRM=0.48, mean (SD)=1.52 (3.16)), and BML+effusion-synovitis (SRM=0.22, mean (SD)=0.65 (2.96)). Alternatively, the unweighted total knee score had the largest IQR of change (IQR=2.49; 25th%=0.12, 75th%=2.61) followed by BML+effusion-synovitis (IQR=1.90; 25th%=-0.43, 75th%=1.47) and cumulative cartilage damage (IQR=0.89; 25th%=0.40, 75th%=1.29).

Associations with Commonly Used KOA Progression Outcomes

Table 4 summarizes the associations between the candidate composite scores and progression in KL, medial JSW, and WOMAC pain. In adjusted models, change in cumulative cartilage damage was the only candidate associated with KL progression (OR=1.84) or JSW progression (OR=2.11). Changes in the unweighted total knee score (OR=1.97) and BML+effusion-synovitis score (OR=1.92) associated with WOMAC knee pain progression.

DISCUSSION

We showed that quantitative composite knee scores using quantitative measurements of cartilage damage, BML, and effusion-synovitis have construct validity with radiographic structural progression (cartilage damage score) and worsening of knee pain (unweighted total score and BML+effusion-synovitis score). We also considered a data-driven approach to identify novel candidate composite scores (e.g., tibial BMLs, patellar pathology); however, these failed to demonstrate adequate performance in the development dataset. Furthermore, despite our presumption that one definition of KOA structural progression may be ideal, we found that 2 composite scores of disease progression may provide a more pragmatic approach to standardize the definitions of KOA progression. By adopting 2 definitions of disease progression – one for cumulative disease burden and another for more dynamic processes related to patient-centered outcomes – we can overcome some significant obstacles to testing disease-modifying therapies for KOA. Specifically, these definitions, and their respective scores, address the multifactorial and complex nature of KOA, represent structural changes in the whole knee, the discordance between structural changes and signs/symptoms/function, and offer a new framework to define KOA progression(3).

This work builds on the potential brought by MR imaging as a powerful outcome tool to measure structures throughout a joint. Thus far, no assessment strategy has met the demand to define structural severity in the whole joint or to reflect changes in important patient-relevant outcomes. Semiquantitative scales have great utility but are insensitive to change(4) and lack a validated composite score to reflect severity in the whole knee(5, 6). To overcome these challenges, we deployed our parsimonious validated methods to quantify cartilage loss, BMLs, and effusion-synovitis, which are clinically relevant features of KOA. Furthermore, the cartilage damage score (representing tibial, femoral, and patellar regions)

and BML+effusion-synovitis score (representing tibial, femoral, and patellar regions and effusion-synovitis throughout the knee) reflect pathological changes throughout the knee. These new composite scores rely on quantitative measurements, which addresses concerns about combining semiquantitative scores to create a whole-knee score(5, 6). Furthermore, these new whole-knee scores offer an alternative to the typical focus on a single region or compartment of the knee (e.g., medial tibiofemoral) with burdensome quantitative methods.

Based on our findings, the cumulative cartilage damage and BML+effusion-synovitis composite scores reflect different constructs of KOA progression. Cumulative cartilage damage represents hyaline cartilage damage throughout the knee, relates to radiographic severity, and reflects the damage attributable to KOA over the course of the disease. The relationship between cartilage damage with radiographic severity complements prior evidence that regional and compartment-specific semiquantitative and quantitative MR-based assessments of cartilage damage progression discriminate and predict structural progression defined by radiographs better than progression in patient-reported outcomes(12, 41, 42). The novelty of the cumulative cartilage damage score is that it is a fully quantitative composite score representing key informative locations throughout the knee, which is optimized to discriminate change. Future studies may clarify if short-term changes in the cumulative cartilage damage score predict long-term symptoms – a hypothesis supported by regional measures of cartilage loss modestly predicting future total knee replacements(43, 44). In contrast to cumulative cartilage damage, the BML+effusion-synovitis composite score may reflect a more dynamic disease activity process that relates to knee pain and reflects a patient’s current state of disease and symptoms. These findings are consistent with prior reports that effusion-synovitis and BMLs relate to changes in patient-reported outcomes(12, 33, 45). The novelty of the BML+effusion-synovitis composite score is that it is a fully quantitative composite score that combines BML volumes and effusion-synovitis volumes throughout the knee to maximize the potential to discriminate change. Overall, these findings are consistent with the heuristic used in other rheumatologic diseases that separately measure damage and disease activity(46).

Our study does have some limitations. Meniscal damage, an important but complex component of KOA, is not included in our composite scores. There is merit in determining the optimal measures of meniscal change among people with KOA and then working on including the meniscus into future composite scores. However, the exclusion of a meniscal measure does not undermine our primary finding that KOA progression may be conceptualized as 2 constructs. Future research will clarify if meniscal measurements contribute to the cumulative damage score or if meniscal changes represent another unique construct of KOA progression. Osteophytes were also not included in our composite scores because their progression is slow and unlikely to change meaningfully in 24 months. We also observed modest AUCs, possibly reflecting the imprecision in using construct validity in the absence of a gold standard for KOA progression. For example, we were limited to using radiographic outcomes focused on the tibiofemoral joint despite our focus on MR-based changes throughout the joint. We also did not account for multiple testing in our significance tests. While we used a sequential testing strategy with development and validation subcohorts to reduce the number of falsely recommended quantitative composite scores, these composite scores need further testing on other data for full validation,

including evaluating the internal consistency of the scores. Finally, we demonstrated that the new composite scores outperform whole-knee BML or effusion-synovitis volumes and relate to radiographic outcomes (e.g., JSW change, KL change). However, future studies are needed to compare these new scores to traditional measures of structural progression (e.g., JSW change, mean cartilage thickness change) in regard to predicting patient-centered outcomes and discriminating group differences in clinical trials.

Our study has several strengths. First, we used a robust, longitudinal cohort with high-quality MR images. Second, we used validated semi-automated quantitative measures of cartilage damage(30, 32), BML volume(33), and effusion-synovitis volume(36–38) that are less burdensome than other measurement methods. Furthermore, these software programs can be disseminated for use by technicians with a modest training requirement. Finally, we used separate development and validation subcohorts for more rigorous validation of the composite knee scores.

In conclusion, we showed that quantitative composite knee scores based on MR measures of cartilage damage, BML, and effusion-synovitis are associated with KOA progression. Our analyses offer a new perspective on KOA progression reflected in the two different domains. First, cumulative damage, which is measured by a cumulative cartilage damage score, is associated with radiographic progression and reflects the damage attributable to KOA over the course of the disease. Second, dynamic disease activity, which is measured by a BML+effusion-synovitis score, relates to changes in a patient's state of disease and symptoms. These domains of KOA progression, and their respective scores, address the multifactorial and complex nature of KOA, the discordance between structural changes and signs/symptoms/function, offer a new framework to define KOA progression, and have promise as MR-based biomarkers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE AND INNOVATION

- 1.** Clinical trials for knee osteoarthritis urgently need quantitative composite whole-knee scores that address 1) the multifactorial and complex etiopathogenesis of knee osteoarthritis, 2) the discordance between structural changes and signs/symptoms/function, and 3) the lack of consensus for the best definitions of disease progression.
- 2.** We offer 2 composite scores that reflect discrete domains of KOA progression.
- 3.** Cumulative damage: the joint damage accrued over time, reflected by a whole-knee cartilage damage score.
- 4.** Disease activity: a patient's state of disease and symptoms that may ebb and flow, reflected by a bone marrow lesion + effusion-synovitis score.

Measurement

Baseline (0-month)

Follow-up (24-months)

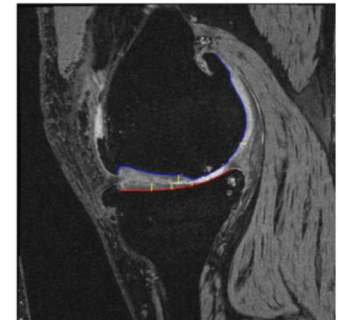
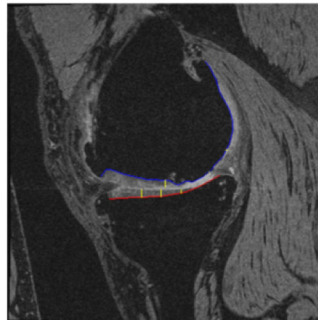
CDI (mm³)

Figure 1: Measurement of medial tibiofemoral cartilage damage index (CDI) on paired baseline and follow-up magnetic resonance (MR) images.

The images are examples of the medial tibiofemoral CDI with cartilage thickness being assessed at 3 out of 9 informative locations (yellow lines) on a tibia (red line) and femur (blue line). These measurements contribute to the whole-knee cumulative cartilage damage.

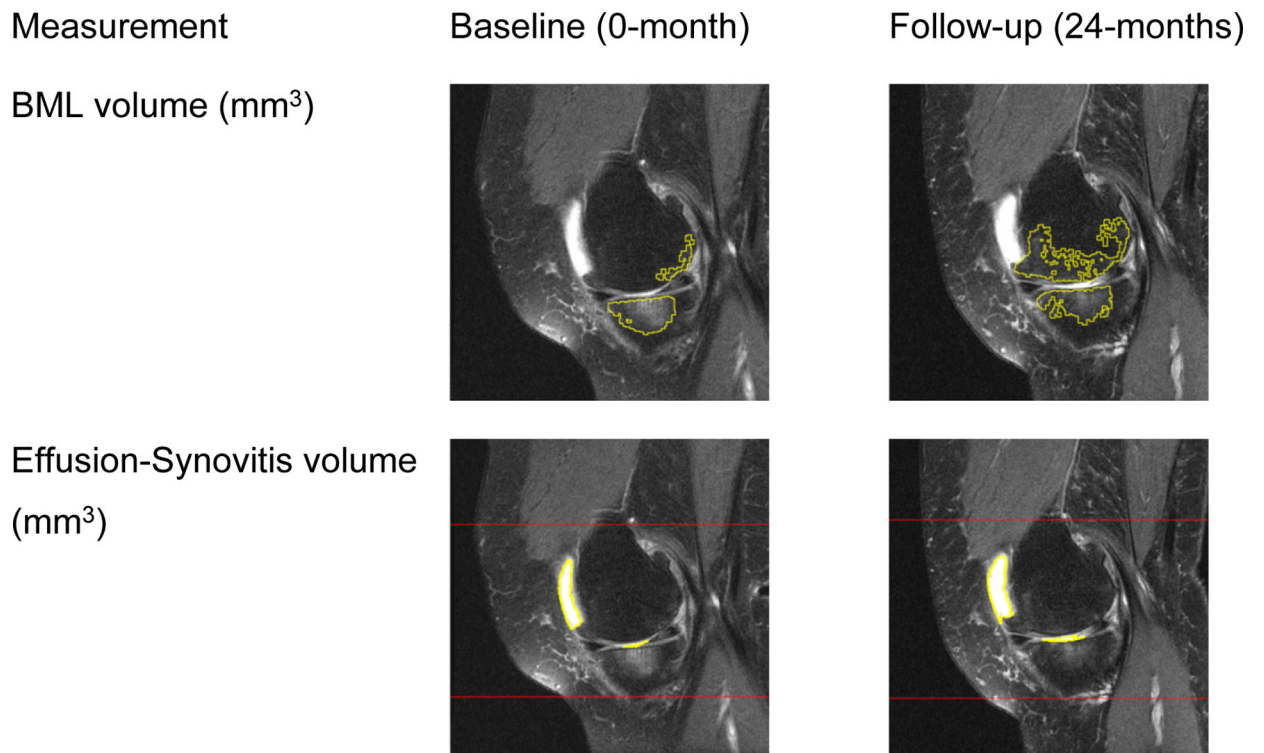


Figure 2: Measurement of medial tibiofemoral bone marrow lesion (BML) and whole knee effusion-synovitis on paired baseline and follow-up magnetic resonance (MR) images. The top row are example MR images of a segmented BML (yellow lines). The bottom row are examples of effusion-synovitis segmentation (yellow lines). These measurements are components of the score based on BML+effusion-synovitis volume.

Table 1:**Binary Outcomes used for Construct Validity Steps in the Development and Validation Cohorts**

Outcome	Details of change from baseline to 24-month visit
<i>Radiographic</i>	
Kellgren-Lawrence Grade Progression	Any change in Kellgren-Lawrence grade
Lateral JSN Progression	Any change in lateral JSN
Medial JSN Progression	Any change in medial JSN
JSN Progression	Any change in medial or lateral JSN
Medial JSW progression	Change median change in the development dataset
<i>Quality of Life</i>	
KQOL 1 improvement	KQOL item 1 improves from 2 worst responses to 3 best responses (how often aware of problems with knee(s))
KQOL 1 worsens	KQOL item 1 worsens from 3 best responses to 2 worst responses (how often aware of problems with knee(s))
KQOL 2 improvement	KQOL item 2 improves from 2 worst responses to 3 best responses (modified lifestyle to avoid potentially damaging activities to knee(s))
KQOL 2 worsens	KQOL item 2 worsens from 3 best responses to 2 worst responses (modified lifestyle to avoid potentially damaging activities to knee(s))
KQOL 3 improvement	KQOL item 3 improves from 2 worst responses to 3 best responses (how much troubled with lack of confidence in knee(s))
KQOL 3 worsens	KQOL item 3 worsens from 3 best responses to 2 worst responses (how much troubled with lack of confidence in knee(s))
KQOL 4 improvement	KQOL item 4 improves from 2 worst responses to 3 best responses (in general, how much difficulty have with knee(s))
KQOL 4 worsens	KQOL item 4 worsens from 3 best responses to 2 worst responses (in general, how much difficulty have with knee(s))
<i>Pain</i>	
WOMAC pain progression	Pain increased by at least 2 points on 0–20 scale
WOMAC pain progression	Pain increased by at least 3 points on 0–20 scale
WOMAC pain improvement	Pain decreased by at least 2 points on 0–20 scale
WOMAC pain improvement	Pain decreased by at least 3 points on 0–20 scale

JSN = joint space narrowing, KQOL = KOOS Quality of Life.

Table 2:

Participant Characteristics

	Development Cohort (n=99)	Validation Cohort (n=197)
Female (n, %)	59 (59.6)	107 (54.3)
Age (years)	61.5 (8.6)	61.2 (8.8)
BMI (kg/m ²)	30.2 (4.6)	30.1 (5.1)
KL grade (n, %)		
0	1 (1.0)	1 (0.5)
1	9 (9.1)	9 (4.6)
2	40 (40.4)	83 (42.1)
3	47 (47.5)	101 (51.3)
4	2 (2.0)	3 (1.5)
Progression, KL grade (n, %)	29 (29.9)	56 (28.9)
Progression, medial JSW (n, %)	47 (47.5)	92 (46.7)
WOMAC Pain, baseline	4.4 (3.6)	5.0 (3.6)
WOMAC Pain, worsen at least 3 points (n, %)	20 (20.2)	31 (15.7)

Reported as mean (SD) unless otherwise indicated. KL progression is any worsening in the KL score. Medial JSW progression is more change than the median change.

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Table 3:

Candidate Quantitative Composite Knee Scores in the Development Cohort

Score	Calculation
Principal Component 1 ^{**}	Sum of CDI in the lateral and medial patella and BML in the medial patella
Principal Component 2 [*]	Sum of BML in lateral and medial tibia
Principal Component 3 [*]	Sum of CDI in the lateral patella, effusion-synovitis volume, and BML in the lateral patella
Principal Component 4 [*]	Sum of CDI in the medial femur and tibia and BML in the medial femur
Principal Component 5 [*]	Sum of BML in lateral femur, medial femur, and lateral patella
Principal Component 6 [*]	Sum of CDI in the lateral femur and tibia
PCA-Weighted Total	Sum of all 13 measurements, weighted by the principal component loading
Inverse variance weighting Total	Sum of all 13 measures, Inverse variance weighted
Unweighted Total ^{**}	Sum of all 13 measurements (simple addition)
Cumulative Cartilage Damage ^{**}	Sum of all 6 CDI measures
BML+Effusion-Synovitis ^{**}	Sum of all 6 BML and effusion-synovitis measures
Whole knee BML volume	Sum of all 6 BML measures
Whole knee Effusion-Synovitis Volume	Sum of all effusion-synovitis volumes

* All knee composite scores based on the principal components analysis are multiplied by the eigenvector for the component and divided by the sum of the eigenvectors of the 6 components.

** Met criteria for further testing in the validation cohort.

PCA = principal component analysis, BML = bone marrow lesion, CDI = cartilage damage index

Table 4:

Odds ratios and Area under the ROC curve for Composite Scores in the Validation Cohort

Knee Measure	Unadjusted		Adjusted*	
	Odds Ratio (95% CI)	AUC	Odds ratio (95% CI)	AUC
Kellgren-Lawrence Grade Progression				
Unweighted total score	1.29 (0.94, 1.77)	0.60	1.38 (0.97, 1.96)	0.71
Cumulative cartilage damage	1.54 (1.12, 2.11)	0.64	1.84 (1.27, 2.69)	0.72
BML+effusion-synovitis	1.17 (0.85, 1.61)	0.59	1.21 (0.86, 1.70)	0.70
Medial Joint Space Width Progression				
Unweighted total score	1.20 (0.90, 1.61)	0.56	1.21 (0.89, 1.64)	0.63
Cumulative cartilage damage	1.93 (1.38, 2.72)	0.67	2.11 (1.44, 3.07)	0.70
BML+effusion-synovitis	1.05 (0.79, 1.39)	0.52	1.05 (0.78, 1.41)	0.63
WOMAC Pain Progression				
Unweighted total score	1.72 (1.18, 2.52)	0.63	1.97 (1.26, 3.08)	0.76
Cumulative cartilage damage	1.28 (0.89, 1.84)	0.55	1.31 (0.86, 1.98)	0.72
BML+effusion-synovitis	1.69 (1.15, 2.48)	0.65	1.92 (1.23, 3.01)	0.76

BML = bone marrow lesion; AUC = area under the ROC curve; 95% CI = 95% confidence intervals.

* Adjusted for age, sex, BMI, race, WOMAC pain, KL, JSW and pain med use.