ACR Open Rheumatology
Vol. 7, No. 9, September 2025, e70085
DOI 10.1002/acr2.70085

American College of Rheumatology
Empowering Rheumatology Professionals

Magnetic Resonance Imaging Biomarkers of Knee Osteoarthritis Progression

Jamie E. Collins,[1] Peter Mesenbrink,[2] Rui Jin,[2] Erik B. Dam,[3] Leticia A. Deveza,[4] Felix Eckstein,[5] Ali Guermazi,[6] Christoph Ladel,[7] Thomas A. Perry,[8] Douglas Robinson,[9] Frank W. Roemer,[10] Christopher J. Swearingen,[11] Wolfgang Wirth,[5] Virginia B. Kraus,[12] and David J. Hunter[4]

Objective. The Foundation for the National Institutes of Health (FNIH) OA Biomarkers Consortium aims to identify, develop, and qualify biomarkers to support drug development in knee osteoarthritis (OA). The project's second phase, the PROGRESS OA study, aims to externally validate prognostic and response biomarkers identified in the earlier phase (phase 1). Here we present results assessing external validation of prognostic imaging biomarkers.

Design. PROGRESS OA included data from the control arms of several completed randomized controlled trials (RCTs) for symptomatic knee OA. Radiographic progression was defined as joint space width loss (JSWL) ≥0.7 mm. Symptomatic progression was defined as increase of nine or more points in Western Ontario and McMaster Universities Arthritis Index pain (0–100 scale). Imaging biomarkers included quantitative measures of cartilage thickness and semiquantitative (SQ) assessments. Associations between baseline biomarkers and outcomes over 12 to 36 months were examined using logistic regression.

Results. A total of 320 participants from four RCTs were included. Forty-one participants (13%) had JSWL ≥0.7 mm and 64 (20%) had worsening symptoms. In univariable logistic regression, measures of quantitative and SQ cartilage, SQ Hoffa-synovitis, effusion-synovitis, and meniscal extrusion were consistently selected to predict JSWL ≥0.7 mm, similar to phase 1. SQ Hoffa-synovitis and lateral meniscal damage were consistently selected to predict symptomatic progression. Cross-validated areas under the curve were 0.69 (95% confidence interval [CI]: 0.53–0.85) for JSWL ≥0.7 mm and 0.77 (95% CI: 0.65–0.87) for symptomatic progression.

Conclusion. The selected prognostic imaging biomarkers are candidates for enriching OA trials for structural and/or symptomatic progressors. Ongoing work includes pursuit of formal biomarker qualification by regulatory agencies, and the use of these biomarkers to capture structural progression with high sensitivity to change.

Supported by the Arthritis Foundation, Biosplice Therapeutics, Inc., Merck KGaA, Novartis, and Pfizer. Dr Collins has received funding for this work from the Foundation for the National Institutes of Health and consulting fees from Boston Imaging Core Lab, LLC. Dr Kraus received a grant from the Foundations for the National Institutes of Health (to her institution) related to this work.

[1]Jamie E. Collins, PhD: Brigham and Women's Hospital, Boston, Massachusetts; [2]Peter Mesenbrink, PhD, Rui Jin, PhD: Novartis Pharmaceuticals Corporation, East Hanover, New Jersy; [3]Erik B. Dam, PhD: Machine Learning Section, Department of Computer Science, University of Copenhagen, Copenhagen, Denmark; [4]Leticia A. Deveza, MD, PhD, David J. Hunter, MBBS, PhD: Sydney Musculoskeletal Health, Kolling Institute, University of Sydney, Sydney, New South Wales, Australia; [5]Felix Eckstein, PhD, Wolfgang Wirth, PhD: Center for Anatomy and Cell Biology and Ludwig Boltzmann Institute for Arthritis and Rehabilitation, Paracelsus Medical University, Salzburg, Austria, and Chondrometrics GmbH, Freilassing, Germany; [6]Ali Guermazi, MD, PhD: Boston University School of Medicine, Boston, and Veterans Affairs Boston Healthcare System, West Roxbury, Massachusetts; [7]Christoph Ladel, PhD: CHL4special consultancy, Darmstadt, Germany; [8]Thomas A. Perry, PhD: Centre for OA Pathogenesis Versus Arthritis, Kennedy Institute of Rheumatology, University of Oxford, Oxford, United Kingdom; [9]Douglas Robinson, PhD: EMD Serono, Billerica, Massachusetts; [10]Frank W. Roemer, MD: Boston University School of Medicine, Boston, Massachusetts, and Department of Radiology, Universitätsklinikum Erlangen & Friedrich Alexander Universität Erlangen-Nürnberg, Erlangen, Germany; [11]Christopher J. Swearingen, PhD: Biometrics, Biosplice Therapeutics, Inc., San Diego, California; [12]Virginia B. Kraus, MD, PhD: Duke Molecular Physiology Institute, Duke University School of Medicine, Durham, North Carolina.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr2. 70085).

Address correspondence via email to Jamie E. Collins, PhD, at Jcollins13@bwh.harvard.edu.

Submitted for publication March 28, 2025; accepted in revised form May 28, 2025.

SIGNIFICANCE & INNOVATION

- Leveraging data from multiple completed randomized controlled trials (RCTs), this study offers a robust external validation of imaging biomarkers, strengthening the evidence for their prognostic value in knee osteoarthritis progression.
- By identifying biomarkers that predict disease progression, this research facilitates patient stratification in RCTs. The results of this study will be used to pursue formal qualification of these biomarkers with regulatory agencies, potentially leading to more efficient studies and personalized treatment strategies.

INTRODUCTION

Knee osteoarthritis (OA) is a common and disabling disease that affects an estimated 14 million people in the United States and 600 million worldwide.[1–3] The disease is characterized by pain and functional impairment and is the leading source of disability in people older than 55 years.[4] Although it is traditionally considered a disease of older age, recent estimates state that more than 8 million of those affected in the United States are under the age of 65, and 2 million are under age 45; the estimated median age of initial knee OA diagnosis is 55 years.[1,5]

Despite the severe clinical and economic impact of OA, no disease-modifying OA drugs (DMOADs) have been approved thus far.[6] Although a number of potential DMOADs have shown promise in preclinical studies, none have succeeded in phase 2 or 3 trials. The reasons these drugs have failed in clinical trials are multifactorial, including a lack of prognostic/predictive biomarkers.[7–9] Structural disease progression in unselected OA populations in clinical trials is slow, and a simple one-fits-all therapeutic approach (that is often applied) dilutes results; thus trials require large sample sizes and/or long follow-up assessments.[10] Biomarkers may allow for more efficient clinical trials. Of particular utility are prognostic biomarkers, used to identify an increased likelihood of a future clinical event or disease progression and to identify and enrich trials for progressors.[11–13] Examples of such prognostic biomarkers include plasma fibrinogen in patients with chronic obstructive pulmonary disease and total kidney volume in patients with polycystic kidney disease.[13,14] The likelihood of a drug reaching approval from phase 1 increases three-fold when patient selection is based on biomarkers versus without.[15]

The Foundation for the National Institutes of Health (FNIH) OA Biomarkers Consortium aims to identify, develop, and qualify biomarkers for regulatory purposes to support drug development in knee OA, including for trial enrichment and for use as clinical trial endpoints accepted by regulatory agencies.[8] Phase 1 of the project encompassed a nested case-control study using data from the Osteoarthritis Initiative (OAI) and sought to determine the prognostic ability of BIPEDS-standard (Burden of Disease, Investigative, Prognostic, Efficacy of Intervention and Diagnostic) biomarkers for the clinical and radiographic progression of knee OA.[16,17] The study found statistically significant associations between a number of baseline imaging biomarkers and subsequent structural and symptomatic disease progression.[18–20]

The findings of phase 1 informed the design of phase 2 of the FNIH OA Biomarkers Consortium, the PROGRESS OA project. The objective of the current project phase was to externally validate these prognostic biomarkers using data from the placebo arms of completed randomized control trials (RCTs).[21] Here we present the results of our analyses that examined the associations between baseline magnetic resonance imaging (MRI)–based biomarkers and clinically relevant knee OA progression over 12 to 36 months.

METHODS

Study design. The PROGRESS OA study includes data from the placebo arms of several completed RCTs that tested various therapeutic interventions for symptomatic knee OA. Four trials were included in this analysis: strontium ranelate (SEKOIA, ISRCTN41323372, Servier, phase 3); lutikizumab (ILLUSTRATE-K, NCT02087904, Abbvie, phase 2a); GLPG1972/S201086 ADAMTS-5 inhibitor (ROCCELLA, NCT03595618, Galapagos, phase 2b); and vitamin D (VIDEO, Arden, ISRCTN 94818153, phase 4).[22–27] The study design and included trials have been described previously and are described briefly here.[21] Participants in each study provided signed informed consent, and all studies were approved by local ethics committee or institutional review board.

All studies aimed to recruit patients with medial compartment knee OA (Kellgren-Lawrence grade [KLG] 2 or 3) and knee pain. The Strontium ranelate Efficacy in Knee Osteoarthritis trial (SEKOIA) trial investigated the effect of strontium ranelate on radiologic and clinical progression of knee OA and included patients meeting American College of Rheumatology (ACR) criteria for knee OA, baseline joint space width (JSW) of 2.5 to 5 mm, predominant knee OA of the medial tibiofemoral compartment, and knee pain.[22,23] A subcohort was selected to undergo MRI.[28] ILLUSTRATE-K evaluated the efficacy and safety of lutikizumab in participants with radiographic evidence of knee OA in the medial femorotibial compartment, knee pain, and synovitis on MRI or ultrasound.[25] ROCCELLA evaluated the efficacy of the ADAMTS-5 inhibitor S201086/GLPG1972 in slowing cartilage loss in knee OA.[26,27] The study included participants fulfilling ACR criteria for knee OA, with medial knee OA (medial joint space narrowing [JSN] greater than lateral JSN), Osteoarthritis Research Society International (OARSI) medial JSN grade 1 or 2, and moderate to severe baseline pain. The VIDEO study evaluated the effect of vitamin D supplementation on the rate of knee OA

progression in participants with knee pain and radiologic evidence of medial knee OA (modified KLG 2 or 3, JSW >1 mm).[24]

For this analysis, we additionally required that participants have baseline and follow-up JSW measurements, baseline semi-quantitative (SQ) assessment of MRI, baseline quantitative measurement of cartilage morphology parameters from MRI, and baseline medial and lateral minimum JSW >0.7 mm.

Endpoints. The primary endpoint was radiographic joint space width loss (JSWL) ≥0.7 mm in the medial femorotibial compartment from baseline to up to a maximum of 36 months of follow-up.[20,29] The primary study endpoint was 24 months; if 24-month JSWL data were not available, then 36-month data were used, otherwise 12-month data were used. Secondary endpoints included pain progression, defined as an increase of nine or more points on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale (0–100 scale, higher score = greater pain), JSWL ≥0.5 mm, the multicomponent endpoints of JSWL ≥0.7 mm and pain progression, and JSWL ≥0.5 mm and pain progression.[21,29,30]

MRI biomarkers. A summary of MRI acquisition for each study is provided in the supplementary materials. MRI biomarkers were assessed at baseline using either quantitative or SQ approaches. All images were evaluated by the same central reading vendors using standardized methods within each individual study and are briefly described here. Quantitative cartilage morphology (thickness, areas, and volume) of the weight-bearing femorotibial joint was measured from manual, quality-controlled cartilage segmentations, performed by experienced readers, of the cartilage surface area and the subchondral bone area, respectively.[31] Areas of full-thickness cartilage loss were counted as having 0 mm cartilage thickness,[18] and results were obtained for the whole joint, compartments, plates (tibia, femur), and subregions.[32] SQ assessment of the whole knee joint was performed using the MRI Osteoarthritis Knee Score (MOAKS) by an experienced radiologist (FWR). Joint features assessed included cartilage, meniscal damage, bone marrow lesions (BMLs), osteophytes, effusion-synovitis, and Hoffa-synovitis. The knee is divided into multiple articular subregions and locations for scoring the different features.[33] Cartilage damage was scored for both the area extent of any cartilage loss (surface area extent) and percentage of full-thickness cartilage loss in a given subregion (0–3 for each score). For surface area extent and size of full-thickness loss, we separately quantified the number of subregions with MOAKS score >0 and the maximum score across all subregions. Osteophyte size was graded from 0 to 3 across 12 locations. BML size was graded from 0 to 3 across 14 subregions. For both osteophytes and BMLs, we quantified the number of locations with score >0 and the maximum score across all locations. Meniscal morphology was scored 0 to 8 (scored on medial and lateral meniscus for the anterior, body and posterior horn): 0 represented no tear/signal abnormality, 2 to 5 reflected different tear types, and 6 to 8 reflected different grades of maceration, ie substance loss. Meniscal extrusion was scored 0 to 3 at four locations; we computed the maximum morphology and the maximum extrusion score across the medial meniscus. Both Hoffa-synovitis and effusion-synovitis were scored 0 to 3. Cartilage morphology, BMLs, and osteophyte scores were summarized over the whole joint and separately for the medial (MFTJ) and lateral tibiofemoral joints and the patellofemoral joint (PFJ).[34] Phase 1 models included scores summarized over the whole joint, and these were used in PROGRESS OA data to validate the phase 1 models. We also considered scores summarized separately by compartment in PROGRESS OA model building.

Statistical analysis. We sought to validate results from the phase 1 study in three sets of analyses, described in detail below. First, we compared associations between individual biomarkers and outcomes in the phase 1 and PROGRESS OA cohorts. Then, we used multivariable regression models to find the best subset of biomarkers to predict outcomes, using data from the PROGRESS OA cohort to determine whether similar sets of biomarkers are selected as in published phase 1 results.[20] Finally, we externally validated the phase 1 multivariable regression models in PROGRESS OA data.

The association between each MRI biomarker and endpoint (structural or symptomatic progression) was assessed first by univariable logistic regression (ie, one biomarker at a time). We compared the association between each biomarker and endpoint in the FNIH phase 1 and PROGRESS OA cohorts.

Using the PROGRESS OA cohort, we used two different modeling approaches to identify the best set of biomarkers to predict endpoints. First, to follow the phase 1 approach, we selected biomarkers with unadjusted values of $P < 0.2$ in univariable analysis and included them in one single multivariable logistic regression model. One-step, backward selection was used to remove potential biomarkers not meeting the nominal inclusion criterion of $P < 0.05$. Sex, baseline age, and baseline body mass index (BMI) were included in all models; the models for JSWL additionally included baseline JSW, whereas the models for pain progression additionally included baseline WOMAC pain score. Multivariable models with covariates only were run for comparison with the models including biomarkers. Areas under the curve (AUCs) were computed with five-fold cross-validation. Odds ratios for continuous variables are presented per 1-SD difference.

Although this approach results in a parsimonious model, it may miss important interactions and may fail to identify important predictors in the presence of multicollinearity.[35] As a second approach, we therefore used a penalized logistic regression model with an elastic net to select the biomarkers that best predicted disease progression. We used 1,000 bootstrap samples to assess associations; odds ratios and 95% confidence intervals (CIs) were derived based on estimates from those 1,000

bootstrap samples. Penalty parameters were selected by grid search given a bootstrap sample. For each biomarker, we determined its frequency of being selected among 1,000 bootstrap samples; the subset of biomarkers selected in >80% of samples was retained.

Because of the large number of MRI biomarkers and the likelihood of multicollinearity, the primary analyses for both the backward selection and elastic net models included a selected set of biomarkers based on the results from phase 1 and expert consensus. The selected set of baseline MRI biomarkers have shown adequate reliability, specificity, and sensitivity and the ability to detect cartilage changes over one to two years,[18–20,36] including the following: quantitative cartilage thickness measured over the total subchondral bone area in the central subregion of the weight-bearing medial femoral condyle, the central subregion of the weight-bearing medial femoral condyle (external), and the total medial femorotibial compartment (MFTC.ThCtAB); SQ biomarkers of cartilage surface area extent and full-thickness loss scores (maximum score, number of subregions with score >0); number of locations affected by any osteophyte; maximum meniscal morphology score; medial meniscus extrusion; Hoffa-synovitis; and effusion-synovitis. A second analysis included all available MRI biomarkers without any preselection; because of the large number of biomarkers and high multicollinearity, these analyses were undertaken with a penalized logistic regression model with an elastic net.

Finally, we sought to validate the regression models from phase 1. Multivariable modeling in phase 1 of the FNIH OA Biomarkers Consortium used three different selection methods to find the best combination of imaging biomarkers to predict radiographic progression over 48 months (see Supplementary Table 3 in Hunter et al.).[20] The published phase 1 models included a combination of the quantitative cartilage thickness measured over the central lateral femur (internal), the medial tibia (external), and the lateral tibia (posterior); SQ osteophytes score (number of locations across the whole knee); SQ full-thickness cartilage loss score (maximum score across whole knee); SQ medial meniscal extrusion score; SQ Hoffa-synovitis score, quantitative medial meniscus volume; and quantitative lateral femoral cartilage volume. Published cross-validated AUCs ranged from 0.716 to 0.723 for the prediction of radiographic progression. Medial meniscus volume and quantitative lateral femoral cartilage volume were not assessed in PROGRESS OA and, therefore, were not included in the model for the validation analysis. We externally validated the three published phase 1 multivariable models by running the models in the PROGRESS OA cohort. We first calculated AUCs and 95% CIs for the phase 1 models (with and without five-fold cross-validation) in phase 1 data, to account for excluding meniscal volume and lateral femoral cartilage volume. We ran these models in the PROGRESS OA data using the regression formula (parameter estimates) derived in phase 1 data, as recommended by the TRIPOD statement.[37] We present AUCs with 95% CIs to assess the discriminative ability of the models. Models were adjusted for age, sex, BMI, and baseline JSW. Analyses were conducted with SAS v9.4 and R packages glmnet, caret, corrplot, Hmisc, MLeval, cutpointr, and data.table.

RESULTS

Across the four RCTs, 320 participants were included in this analysis: 53 from ILLUSTRATE-K, 166 from ROCCELLA, 88 from SEKOIA, and 13 from VIDEO. They were 58% female, with an average age ± SD of 62.7 ± 7.5 years, 37% had KLG 2, and 63% had KLG 3 (Table 1). Forty-one participants (13%) met the primary endpoint of JSWL ≥0.7 mm; 72 (23%) met the secondary endpoint of JSWL ≥0.5 mm; and 64 (20%) met the secondary endpoint of WOMAC pain progression of nine or more points. Twelve participants (4%) met the combined endpoint of JSWL ≥0.7 mm and WOMAC pain progression nine or more points, and 18 (6%) met the combined endpoint of JSWL ≥0.5 mm and WOMAC pain progression nine or more points. Because of the small number with combined JSWL and pain progressors, further analysis was not performed on this endpoint. The percent meeting the primary endpoint of JSWL ≥0.7 mm ranged from 2% in ILLUSTRATE-K to 18% in SEKOIA. Descriptive statistics by study for cohort characteristics and all endpoints are provided in Supplementary Table S1.

Clinical characteristics of PROGRESS OA (phase 2) vs FNIH phase 1. A comparison of cohort demographic and clinical characteristics between FNIH phase 1 and PROGRESS OA is shown in Supplementary Table S2. The cohorts were similar with respect to age, sex, and BMI. The PROGRESS OA cohort had

Table 1. Cohort Characteristics*

Characteristic	Value
Sex, n (%)	
Female	185 (58)
Male	135 (42)
Age, mean ± SD, y	62.7 ± 7.5
BMI, mean ± SD	29.8 ± 4.7
Race, n (%)	
Asian	26 (8)
Black	20 (6)
Other	4 (1)
White	270 (84)
Knee laterality, n (%)	
Left	170 (53)
Right	150 (47)
Baseline KLG, n (%)	
2	119 (37)
3	201 (63)
Baseline Medial JSW, mean ± SD, mm	3.0 ± 1.0
Baseline WOMAC pain (0–100, 100 worst), mean ± SD	46.7 ± 18.8

*BMI, body mass index; KLG, Kellgren-Lawrence grade; JSW, joint space width; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

more advanced OA at baseline: 63% KLG3 versus 37% in FNIH phase 1.

Comparison of associations between MRI biomarkers and measures of disease progression. Descriptive statistics and results of univariable regression analyses for the selected set of MRI biomarkers are shown for both FNIH phase 1 and PROGRESS OA in Table 2. Results were generally similar between the two cohorts, with odds ratios in the same direction and similar in magnitude. For example, a 1-SD greater baseline mean cartilage thickness over the central weight-bearing medial femoral condyle (ccMF) was associated with a 0.65-times decreased odds of JSWL ≥0.7 mm in PROGRESS OA (95% CI: 0.47–0.88) versus a 0.75-times decreased odds of JSWL ≥0.7 mm in FNIH phase 1 (95% CI: 0.63–0.88). Baseline SQ medial meniscal morphology score >5 (maceration) was associated with a 2.2-times increased odds of JSWL ≥0.7 mm in both PROGRESS OA (95% CI: 0.8–5.9) cohorts and FNIH phase 1 (95% CI: 1.5–3.2).

Multivariable models for disease progression in PROGRESS OA (phase 2). Univariable associations between the selected set of biomarkers and JSWL ≥0.7 mm are shown in Figure 1. After backward selection, the final multivariable model included SQ medial meniscal extrusion, SQ cartilage surface area extent score (max score in the MFTJ), and quantitative cartilage thickness over the ccMF (Table 3). The cross-validated AUC for this model was 0.69 (95% CI: 0.53–0.85). A summary of elastic net selection is provided in Table 4. In elastic net models, the following MRI biomarkers were selected in all bootstrap samples: SQ medial meniscal extrusion, SQ cartilage surface area extent score (max score MFTJ), SQ cartilage full-thickness loss score (max score PFJ), SQ effusion-synovitis, SQ Hoffa-synovitis, and quantitative cartilage thickness over the cc.MF. Quantitative cartilage thickness over MFTC was selected in approximately 90% of bootstrap samples. The cross-validated AUC for the model, including all seven biomarkers, was 0.69 (95% CI: 0.56–0.82). The cross-validated AUC for the model with covariates only was 0.48 (95% CI: 0.43–0.52).

Univariable associations between biomarkers and JSWL ≥0.5 mm are shown in Supplementary Figure S1. The final multivariable model selected using backward selection logistic regression included SQ Hoffa-synovitis. The model AUC was 0.57 (95% CI: 0.43–0.78) (Table 3). In elastic net modeling, SQ effusion-synovitis and SQ Hoffa-synovitis were selected in >80% of bootstrap samples (Table 4). The AUC for the model including all nine biomarkers was 0.60 (95% CI: 0.44–0.73). The cross-validated AUC for the model with covariates only was 0.52 (95% CI: 0.47–0.56).

Univariable associations between biomarkers and WOMAC pain progression are shown in Supplementary Figure S2. The final multivariable model selected using backward selection logistic regression included SQ Hoffa-synovitis and SQ lateral meniscal morphology. The model AUC was 0.77 (Table 3). In elastic net modeling the following variables were selected in >80% of bootstrap samples: SQ medial meniscal extrusion, SQ medical meniscal root tear, SQ lateral meniscal morphology, SQ effusion-synovitis, SQ Hoffa-synovitis, SQ cartilage full-thickness loss score (number of subregions with score >0) in the PFJ, and quantitative cartilage thickness over the MFTC.ThCtAB. The AUC for the model, including all five biomarkers, was 0.78 (95% CI: 0.67–0.88). The cross-validated AUC for the model with covariates only was 0.71 (95% CI: 0.70–0.74).

Table 4 shows the results of penalized regression with elastic net for models with the selected set of biomarkers (columns 2–4) and for models using all biomarkers (columns 5–7). For all outcomes, AUCs were similar between the two approaches, as were biomarkers selected (Table 4). For the primary outcome of JSWL ≥0.7 mm, additional measures of quantitative cartilage were selected in models using all biomarkers.

Validating phase 1 regression models in PROGRESS OA (phase 2). We assessed the performance of three published phase 1 regression models (Supplementary Table S3). First we ran the updated models, excluding parameters not available in PROGRESS OA, in phase 1 data. Cross-validated AUCs ranged from 0.70 to 0.72. The full phase 1 regression model (model 1), which uniquely included medial meniscal extrusion score in addition to parameters of models 2 and 3, performed well in PROGREESS OA data, with an AUC of 0.67. AUCs for model 2 (model 3 parameters plus Hoffa-synovitis and full-thickness cartilage loss scores) and model 3 (cartilage thickness of the central lateral femur, medial tibia, and lateral tibia in addition to osteophyte score) were modest, yielding AUCs of 0.61 and 0.58, respectively.

DISCUSSION

In this external validation of MRI-based prognostic biomarkers for knee OA progression, we found similar associations, in both direction and magnitude, between baseline MRI biomarkers and radiographic disease progression as in the original FNIH phase 1 study. Measures of quantitative and SQ cartilage, SQ Hoffa-synovitis and effusion-synovitis, and SQ meniscal extrusion were consistently selected across all models for the primary endpoint of JSWL ≥0.7 mm. In addition, the full phase 1 regression formula demonstrated modest discrimination, yielding an AUC of 0.67.

Here we sought to externally validate a set of MRI-based prognostic biomarkers identified in prior analyses of the FNIH phase 1 cohort.[18–20] Other studies have used machine learning approaches to identify important biomarkers and imaging characteristics in the FNIH phase 1 cohort. Nelson et al used a machine learning approach to identify features associated with composite

Table 2. Comparison of individual MRI biomarkers in FNIH phase 1 vs PROGRESS OA*

	FNIH phase 1, JSWL >0.7 mm over 48 mo			PROGRESS OA, JSWL >0.7 mm over 12–36 mo		
	No, n = 303	Yes, n = 297	OR (95% CI)	No, n = 279	Yes, n = 41	OR (95% CI)
Q mean cartilage thickness ccMF.ThCtAB	2.0 ± 0.5	1.8 ± 0.6	0.75 (0.63–0.88)	1.6 ± 0.5	1.4 ± 0.6	0.63 (0.45–0.87)
Q mean cartilage thickness ecMF.ThCtAB	1.3 ± 0.3	1.3 ± 0.4	0.78 (0.66–0.92)	1.2 ± 0.3	1.1 ± 0.4	0.81 (0.59–1.12)
Q mean cartilage thickness MFTC.ThCtAB	3.4 ± 0.6	3.3 ± 0.6	0.90 (0.77–1.06)	3.0 ± 0.5	2.8 ± 0.7	0.73 (0.53–1.00)
SQ cartilage surface area extent: maximum score						
0–1	25 (8)	15 (5)	REF	4 (1)	0 (0)	REF
2	216 (71)	214 (72)	1.7 (0.8–3.2)	156 (56)	12 (29)	
3	62 (20)	68 (23)	1.8 (0.9–3.7)	119 (43)	29 (71)	3.2 (1.6–6.6)
SQ cartilage full-thickness damage: maximum score						
0	95 (31)	55 (19)	REF	59 (21)	5 (12)	REF
1	55 (18)	72 (24)	2.3 (1.4–3.6)	35 (13)	6 (15)	2.0 (0.6–7.1)
2	136 (45)	154 (52)	2.0 (1.3–3.0)	159 (57)	21 (51)	1.6 (0.6–4.3)
3	17 (6)	16 (5)	1.6 (0.8–3.5)	26 (9)	9 (22)	4.1 (1.2–13.4)
SQ cartilage surface area extent: number of SR with damage						
0–1	33 (11)	12 (4)	REF	5 (1)	0 (0)	REF
2–4	137 (45)	93 (31)	1.9 (0.9–3.9)	68 (25)	4 (10)	
5–7	110 (36)	139 (47)	3.5 (1.7–7.0)	131 (47)	23 (56)	3.2 (1.1–9.6)
8+	23 (8)	53 (18)	6.3 (2.8–14.4)	75 (27)	14 (34)	3.4 (1.1–10.8)
SQ cartilage full-thickness damage: number of SR with damage						
0	95 (31)	55 (19)	REF	59 (21)	5 (12)	REF
1–2	146 (48)	146 (49)	1.7 (1.2–2.6)	95 (34)	10 (24)	1.2 (0.4–3.8)
3+	62 (20)	96 (32)	2.7 (1.7–4.3)	125 (45)	26 (63)	2.5 (0.9–6.7)
SQ osteophytes: number of locations with osteophyte						
0–2	63 (21)	32 (11)	REF	71 (25)	6 (15)	REF
3–5	95 (31)	64 (22)	1.3 (0.8–2.2)	81 (29)	15 (37)	2.2 (0.8–6.0)
6+	145 (48)	201 (68)	2.7 (1.7–4.4)	127 (46)	20 (49)	1.9 (0.7–4.9)
SQ medial meniscal extrusion						
0: <2 mm	123 (41)	110 (37)	REF	60 (22)	0 (0)	REF
1: 2–2.9 mm	134 (44)	116 (39)	1.6 (1.1–2.4)	72 (26)	11 (27)	
2: 3–4.9 mm	37 (12)	60 (20)	2.2 (1.4–3.3)	89 (32)	14 (34)	1.9 (0.8–4.3)
3: > 5mm	9 (3)	11 (4)	5.0 (2.5–9.7)	58 (21)	16 (39)	3.3 (1.4–7.6)
SQ meniscal morphology medial						
0–1 (no tear)	154 (51)	99 (33)	REF	60 (22)	4 (10)	REF
2–5 (tear)	79 (26)	100 (34)	2.0 (1.3–2.9)	57 (20)	8 (20)	2.1 (0.6–7.4)
6–8 (maceration)	70 (23)	98 (33)	2.2 (1.5–3.2)	162 (58)	29 (71)	2.7 (0.9–8.0)
SQ synovitis-effusion						
0–1	257 (85)	226 (76)	REF	214 (77)	24 (59)	REF
2–3	46 (15)	71 (24)	1.8 (1.2–2.6)	65 (23)	17 (41)	2.3 (1.2–4.6)
SQ Hoffa-synovitis						
0	150 (50)	96 (32)	REF	92 (33)	8 (20)	REF
1	134 (44)	168 (57)	2.0 (1.4–2.8)	157 (56)	23 (56)	1.7 (0.7–3.9)
2–3	19 (6)	33 (11)	2.7 (1.5–5.1)	30 (11)	10 (24)	3.8 (1.4–10.6)

*Mean ± SD shown for continuous variables, n (%) for categorical variables. ORs are shown per 1 SD for continuous variables. ccMF.ThCtAB, central weight-bearing medial femoral condyle; CI, confidence interval; ecMF.ThCtAB, central medial femoral condyle (external); JSWL, joint space width loss; MFTC.ThCtAB, total medial femorotibial compartment; OR, odds ratio; Q, quantitative; REF, reference; SQ, semiquantitative; SR, subregion.

structural and pain progression endpoints[38]; the selected imaging features included BMLs, osteophytes, and medial meniscal extrusion. Osteophytes and meniscal extrusion were features identified in our phase 1 analyses; although both were associated with progression in univariable analyses, only meniscal extrusion was consistently selected in multivariable modeling. Deng et al used LASSO regression to create a quantitative cartilage risk score and reported an AUC 0.69 for predicting combined structural

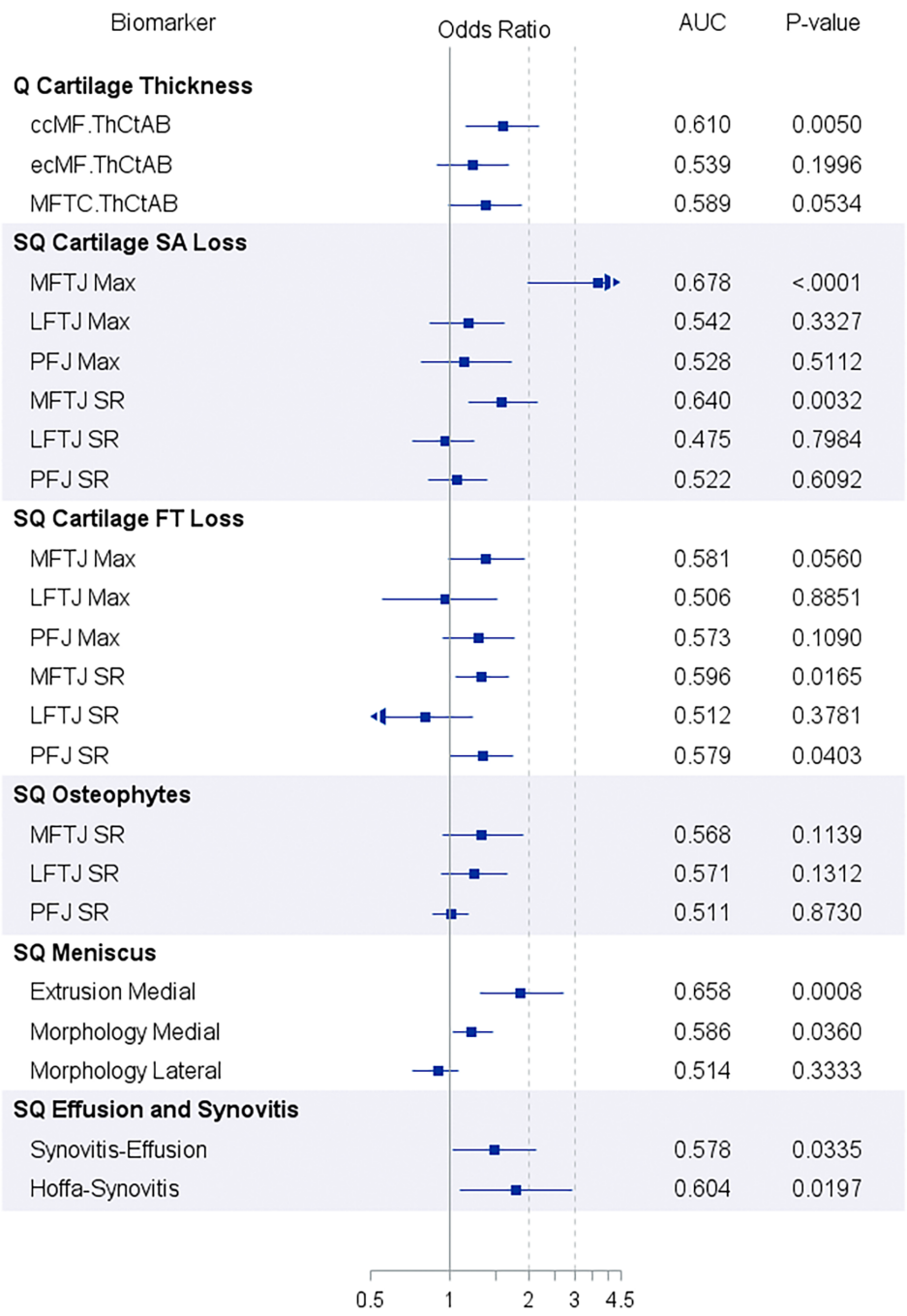

Figure 1. Univariable associations between the primary set of baseline magnetic resonance imagin biomarkers and joint space width loss ≥0.7 mm in PROGRESS OA. The results from unadjusted univariable logistic regression are shown for each biomarker. Individual biomarkers are shown along the y-axis and unadjusted odds ratios with 95% confidence intervals are shown along the x-axis. The x-axis is on the log scale. *P* values and AUCs for each biomarker are shown in the columns on the right. AUC, area under the curve; ccMF.ThCtAB, central weight-bearing medial femoral condyle; ecMF.ThCtAB, central medial femoral condyle (external); LFTJ, lateral tibiofemoral joint; MFTC.ThCtAB, total medial femorotibial compartment; MFTJ, medial tibiofemoral joint; PFJ, patellofemoral joint; Q, quantitative; SQ, semiquantitative; SR, subregion.

and symptomatic progression.[39] Quantitative measures of cartilage thickness were consistently selected as important predictors in our analysis.

Like the FNIH OA Biomarkers Consortium, the IMI-APPROACH study aimed to develop and validate prognostic imaging and biochemical biomarkers for knee OA progression in a European cohort.[40,41] Participants were selected from ongoing cohort studies of knee OA and enrolled into the 2-year APPROACH study. A machine learning algorithm was used to select participants with a high likelihood of JSWL or pain progression.[42] The enrichment algorithm for structural progression had modest discrimination (AUC 0.61), and the algorithm for pain

Table 3. Results of logistic regression with backward selection to predict primary and secondary endpoints with baseline MRI biomarker features*

Endpoint	AUC[a] (95% CI)	MRI biomarkers included (measured at baseline)	Odds ratio (95% CI)
JSWL ≥0.7 mm	0.69 (0.53–0.85)	SQ medial meniscal extrusion	2.04 (1.23–3.43)
		SQ cartilage surface area extent score: maximum score in the MFTJ	3.36 (1.53–7.55)
		Q thickness of the cartilage over the ccMF.ThCtAB	0.33 (0.13–0.82)
JSWL ≥0.5 mm	0.57 (0.43–0.78)	SQ Hoffa-synovitis	1.79 (1.18–2.75)
WOMAC Pain ≥9 points (0–100 scale)	0.77 (0.65–0.87)	SQ lateral meniscal morphology	2.06 (1.28–3.31)
		SQ Hoffa-synovitis	2.02 (1.22–3.42)

*Models were additionally adjusted for age, sex, body mass index, baseline joint space width (JSWL models), baseline pain (WOMAC pain progression models). AUC, area under the curve; CI, confidence interval; Q, quantitative; JSWL, joint space width loss; MRI, magnetic resonance imaging; SQ, semiquantitative; WOMAC, Western Ontario and McMaster Universities Arthritis Index.
[a]5-fold cross-validated AUCs.

progression performed well (AUC 0.82).[43] In our study, we found that the regression model developed in phase 1 for predicting radiographic progression yielded AUC 0.67 when deployed in PROGRESS OA.

It is encouraging that we found similar associations between prognostic biomarkers and progression in this external validation study and that the phase 1 multivariable regression model performed reasonably well (AUC 0.67 in phase 2 data vs 0.72 in phase 1 data), despite marked differences in the FNIH phase 1 and PROGRESS OA cohorts, particularly with regard to the severity of baseline radiographic OA. Phase 1 was a nested case-control study within the OAI, and by design and case

Table 4. Results of elastic net selection to predict primary and secondary outcomes with baseline MRI biomarker features*

MRI biomarkers selected in >80% of bootstrapped samples	Prespecified selected set			All biomarkers		
	JSWL ≥0.7 mm	JSWL ≥0.5 mm	WOMAC Pain ≥9	JSWL ≥0.7 mm	JSWL ≥0.5 mm[a]	WOMAC Pain ≥9
SQ cartilage surface area score: max score MFTJ	x			x		
SQ full-thickness cartilage damage score: max score PFJ	x					x
SQ full-thickness cartilage damage score: number of SR with full-thickness loss PFJ			x	x		
SQ BML: number of SR with BML size score >0 MFTJ				x		
SQ Hoffa-synovitis	x	x	x	x		x
SQ effusion-synovitis	x	x	x	x		x
SQ medial meniscal extrusion	x		x	x		x
SQ lateral meniscal morphology			x			
SQ meniscal root tear: medial			x			
Q cartilage thickness MFTC.ThCtAB	x		x			
Q mean cartilage thickness central subregion of central medial femur (ccMF.ThCtAB)	x			x		
Q maximal cartilage thickness over the central lateral femur (cLF.ThCtAB.aMav)				x		
Q total area of subchondral bone medial tibia				x		
Q cartilage volume over the central lateral femur				x		
Q cartilage surface area over the central lateral femur				x		
Q denuded area in percent of the tAB: external subregion of central medial femur						x
Model AUC (95% CIs)	0.69 (0.56–0.82)	0.60 (0.44–0.73)	0.78 (0.67–0.88)	0.70 (0.49–0.90)	0.55 (0.42–0.69)	0.78 (0.68–0.87)

*AUC, area under the curve; BML, bone marrow lesion; ccMF, central subregion of the weight-bearing medial femoral condyle; CI, confidence interval; cLF, central lateral femur; JSWL, joint space width loss; MFTC, total medial femorotibial compartment; MFTJ, medial tibiofemoral joint; MRI, magnetic resonance imaging; PFJ, patellofemoral joint; Q, quantitative; SQ, semiquantitative; SR, subregion; tAB, total subchondral bone area; ThCtAB, Mean cartilage thickness over the entire tAB; ThCtAB.aMav, maximal cartilage thickness over the entire tAB; WOMAC, Western Ontario and McMaster Universities Arthritis Index.
[a]No biomarkers selected in elastic net. AUC of 0.55 represents covariate-only model.

selection, 50% of the participants had radiographic progression compared to only 13% in PROGRESS OA. Differences in endpoint rate are due not only to study design but also study duration: progression in phase 1 was measured over up to 48 months, whereas the majority of PROGRESS OA participants had endpoints assessed at 12 months. The PROGRESS OA cohort had, on average, more severe disease at baseline (higher KLG and JSN grade, smaller JSW, more severe pain), reflecting a typical DMOAD trial population. Although some biomarkers were statistically significantly associated with progression in phase 1 but not in PROGRESS OA, caution should be used in comparing *P* values between the studies due to differences in sample sizes and endpoint rate; the power to detect statistically significant associations was lower in PROGRESS OA compared to FNIH phase 1. Similar findings, despite these differences, underscore the robustness of these prognostic markers and models. However, we also recognize that AUCs in the range of approximately 0.7 are generally considered modest and that interpreting clinical usefulness is challenging.[44,45]

This study has several limitations. Interpreting longitudinal pain data from the placebo arms of RCTs is challenging; pain reporting is subject to placebo and contextual effects and regression to the mean.[46,47] Sixty-four (20%) participants met the definition of pain progression of a nine-or-more-point increase, but only 12 (4%) experienced both structural (JSWL ≥0.7 mm) and symptomatic progression. This sample size thus precluded analysis of the combined structural and pain progression endpoint and, therefore, direct comparison to the primary endpoint of the phase 1 study. Although the included trials had generally similar inclusion and exclusion criteria, there were key differences, notably in the trial length. Participants in trials of longer duration (SEKOIA, VIDEO) had more opportunity to progress; however, almost 70% of included participants had the radiographic progression endpoint measured at 12 months (ROCELLA). We may have observed a greater proportion of participants reaching the study endpoints if we had included trials with longer follow-up duration. Inclusion criteria for ILLUSTRATE-K included evidence of synovitis on MRI or ultrasound; thus participants with OA synovitis could be oversampled in PROGRESS OA. The sample was 84% White, limiting our ability to generalize to other races or ethnicities. The initial goal of this study was to investigate the combination of biochemical and imaging biomarkers to predict clinically relevant progression, as explored in phase 1.[20,21] However, only one trial (VIDEO) included both biochemical and imaging biomarkers, but its sample size was too small (n = 13) to support this combined analysis.

Whether and when an enrichment algorithm or prognostic biomarker will increase trial efficiency depends on its ability to accurately predict progression.[48] Future work will consider which definitions or thresholds for "high risk" provide the most efficient enrichment strategy. The relatively modest rate of progression underscores the challenge of DMOAD trials: an endpoint with 13% incidence in the placebo group would require a sample size of 326 per group to have >80% power to demonstrate a two-fold increased risk of progression in the placebo group (ie, 6.5% vs 13%) or a sample size of 807 per group to demonstrate a 50% increase in risk (ie, 8.7% vs 13%).

We focused here on prognostic biomarkers, which are used to identify the increased likelihood of a future clinical event or disease progression. A key aim of PROGRESS OA is to assess short-term change in biomarkers as potential response biomarkers (ie, surrogate endpoints).[13,21] Several recent RCTs have included quantitative cartilage morphometry as an outcome measure.[49] Analyses from phase 1 found combinations of short-term change in imaging biomarkers that could predict progression with high accuracy with AUCs ranging from 0.68 to 0.71 for combined radiographic and symptom progression and 0.79 to 0.83 for radiographic progression.[20] Externally validating these results in PROGRESS OA will be a focus of future work.

In conclusion, we externally validated a set of prognostic MRI-based biomarkers for knee OA progression and found similar associations, both in direction and in magnitude, in the original FNIH phase 1 cohort and the independent PROGRESS OA study cohort. The combination of quantitative cartilage thickness and SQ measures of cartilage damage, meniscus, and synovitis were consistently selected in both cohorts across a range of modeling strategies. The selected MRI-based prognostic biomarkers may be candidates for enriching OA trials for progressors. Ongoing work includes pursuit of formal biomarker qualification, and the use of these biomarkers to capture structural progression with high sensitivity to change.

CONFLICTS OF INTEREST

Scientific and financial support for the FNIHBiomarkers Consortium PROGRESS OA study is made possible through grants and direct and in-kind contributions provided by the following: Arthritis Foundation; Biosplice The rapeutics Inc.; Merck KGaA, Darmstadt, Germany; Novartis; Pfizer.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Collins confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Deshpande BR, Katz JN, Solomon DH, et al. Number of persons with symptomatic knee osteoarthritis in the US: impact of race and

ethnicity, age, sex, and obesity. Arthritis Care Res (Hoboken) 2016; 68(12):1743–1750.

2. Disease GBD, Injury I, Prevalence C; GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017; 390(10100):1211–1259.
3. Steinmetz JD, Culbreth GT, Haile LM, et al; GBD 2021 Osteoarthritis Collaborators. Global, regional, and national burden of osteoarthritis, 1990-2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Rheumatol 2023;5(9): e508–e522.
4. Barbour KE, Helmick CG, Boring M, et al. Vital Signs: prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation - United States, 2013-2015. MMWR Morb Mortal Wkly Rep 2017; 66(9):246–253.
5. Losina E, Weinstein AM, Reichmann WM, et al. Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US. Arthritis Care Res (Hoboken) 2013;65(5):703–711.
6. Oo WM, Little C, Duong V, et al. The development of disease-modifying therapies for osteoarthritis (DMOADs): the evidence to date. Drug Des Devel Ther 2021;15:2921–2945.
7. Karsdal MA, Michaelis M, Ladel C, et al. Disease-modifying treatments for osteoarthritis (DMOADs) of the knee and hip: lessons learned from failures and opportunities for the future. Osteoarthritis Cartilage 2016; 24(12):2013–2021.
8. Hunter DJ, Nevitt M, Losina E, et al. Biomarkers for osteoarthritis: current position and steps towards further validation. Best Pract Res Clin Rheumatol 2014;28(1):61–71.
9. Kim JS, Borges S, Clauw DJ, et al. FDA/Arthritis Foundation osteoarthritis drug development workshop recap: assessment of long-term benefit. Semin Arthritis Rheum 2022;56:152070.
10. Kraus VB, Burnett B, Coindreau J, et al; OARSI FDA Osteoarthritis Biomarkers Working Group. Application of biomarkers in the development of drugs intended for the treatment of osteoarthritis. Osteoarthritis Cartilage 2011;19(5):515–542.
11. Kraus VB. Biomarkers as drug development tools: discovery, validation, qualification and use. Nat Rev Rheumatol 2018;14(6):354–362.
12. Robb MA, McInnes PM, Califf RM. Biomarkers and surrogate endpoints: developing common terminology and definitions. JAMA 2016;315(11):1107–1108.
13. FDA-NIH Biomarker Working Group. BEST. (Biomarkers, EndpointS, and other Tools) Resource. National Institutes of Health; 2016.
14. Miller BE, Tal-Singer R, Rennard SI, et al; Perspective of the Chronic Obstructive Pulmonary Disease Biomarker Qualification Consortium. Plasma fibrinogen qualification as a drug development tool in chronic obstructive pulmonary disease. Perspective of the chronic obstructive pulmonary disease biomarker qualification consortium. Am J Respir Crit Care Med 2016;193(6):607–613.
15. Thomas DBJ, Audette J, Carroll A, et al. *Clinical Development Success Rates 2006-2015*. Biotechnology Innovation Organization; 2016.
16. Kraus VB, Collins JE, Hargrove D, et al; OA Biomarkers Consortium. Predictive validity of biochemical biomarkers in knee osteoarthritis: data from the FNIH OA Biomarkers Consortium. Ann Rheum Dis 2017;76(1):186–195.
17. Bauer DC, Hunter DJ, Abramson SB, et al; Osteoarthritis Biomarkers Network. Classification of osteoarthritis biomarkers: a proposed approach. Osteoarthritis Cartilage 2006;14(8):723–727.
18. Eckstein F, Collins JE, Nevitt MC, et al; FNIH OA Biomarkers Consortium. Brief report: cartilage thickness change as an imaging biomarker of knee osteoarthritis progression: data from the Foundation for the National Institutes of Health Osteoarthritis Biomarkers Consortium. *Arthritis* Rheumatol 2015;67(12):3184–3189.
19. Collins JE, Losina E, Nevitt MC, et al. Semiquantitative imaging biomarkers of knee osteoarthritis progression: data from the Foundation for the National Institutes of Health Osteoarthritis Biomarkers Consortium. Arthritis Rheumatol 2016;68(10):2422–2431.
20. Hunter DJ, Deveza LA, Collins JE, et al. Multivariable modeling of biomarker data from the phase I Foundation for the National Institutes of Health Osteoarthritis Biomarkers Consortium. Arthritis Care Res (Hoboken) 2022;74(7):1142–1153.
21. Hunter DJ, Collins JE, Deveza L, et al. Biomarkers in osteoarthritis: current status and outlook - the FNIH Biomarkers Consortium PROGRESS OA study. Skeletal Radiol 2023;52(11):2323–2339.
22. Reginster JY, Badurski J, Bellamy N, et al. Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind, randomised placebo-controlled trial. Ann Rheum Dis 2013;72(2):179–186.
23. Cooper C, Reginster JY, Chapurlat R, et al. Efficacy and safety of oral strontium ranelate for the treatment of knee osteoarthritis: rationale and design of randomised, double-blind, placebo-controlled trial. Curr Med Res Opin 2012;28(2):231–239.
24. Arden NK, Cro S, Sheard S, et al. The effect of vitamin D supplementation on knee osteoarthritis, the VIDEO study: a randomised controlled trial. Osteoarthritis Cartilage 2016;24(11):1858–1866.
25. Fleischmann RM, Bliddal H, Blanco FJ, et al. A phase II trial of lutikizumab, an anti-interleukin-1α/β dual variable domain immunoglobulin, in knee osteoarthritis patients with synovitis. Arthritis Rheumatol 2019; 71(7):1056–1069.
26. Schnitzer T, Pueyo M, Deckx H, et al. Evaluation of S201086/GLPG1972, an ADAMTS-5 inhibitor, for the treatment of knee osteoarthritis in ROCCELLA: a phase 2 randomized clinical trial. Osteoarthritis Cartilage 2023;31(7):985–994.
27. Imbert O, Deckx H, Bernard K, et al. The design of a randomized, placebo-controlled, dose-ranging trial to investigate the efficacy and safety of the ADAMTS-5 inhibitor S201086/GLPG1972 in knee osteoarthritis. Osteoarthr Cartil Open 2021;3(4):100209.
28. Pelletier JP, Roubille C, Raynauld JP, et al. Disease-modifying effect of strontium ranelate in a subset of patients from the phase III knee osteoarthritis study SEKOIA using quantitative MRI: reduction in bone marrow lesions protects against cartilage loss. Ann Rheum Dis 2015;74(2):422–429.
29. Hunter D, Nevitt M, Lynch J, et al; FNIH OA Biomarkers Consortium. Longitudinal validation of periarticular bone area and 3D shape as biomarkers for knee OA progression? Data from the FNIH OA Biomarkers Consortium. Ann Rheum Dis 2016;75(9):1607–1614.
30. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. Arthritis Rheum 2001;45(4):384–391.
31. Eckstein F, Wluka AE, Wirth W, et al. 30 Years of MRI-based cartilage & bone morphometry in knee osteoarthritis–from correlation to clinical trials. Osteoarthritis Cartilage. 2024;32(4):439–451.
32. Wirth W, Eckstein F. A technique for regional analysis of femorotibial cartilage thickness based on quantitative magnetic resonance imaging. IEEE Trans Med Imaging 2008;27(6):737–744.
33. Hunter DJ, Guermazi A, Lo GH, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage 2011;19(8):990–1002.
34. Roemer FW, Jansen M, Marijnissen ACA, et al. Structural tissue damage and 24-month progression of semi-quantitative MRI biomarkers of knee osteoarthritis in the IMI-APPROACH cohort. BMC Musculoskelet Disord 2022;23(1):988.

35. Austin PC, Tu JV. Automated variable selection methods for logistic regression produced unstable models for predicting acute myocardial infarction mortality. J Clin Epidemiol 2004;57(11):1138–1146.
36. Roemer FW, Guermazi A, Collins JE, et al. Semi-quantitative MRI biomarkers of knee osteoarthritis progression in the FNIH biomarkers consortium cohort - methodologic aspects and definition of change. BMC Musculoskelet Disord 2016;17(1):466.
37. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015;162(1): W1–73.
38. Nelson AE, Fang F, Arbeeva L, et al. A machine learning approach to knee osteoarthritis phenotyping: data from the FNIH Biomarkers Consortium. Osteoarthritis Cartilage 2019;27(7):994–1001.
39. Deng C, Sun Y, Zhang Z, et al. Development and evaluation of nomograms for predicting osteoarthritis progression based on MRI cartilage parameters: data from the FNIH OA biomarkers Consortium. BMC Med Imaging 2023;23(1):43.
40. van Helvoort EM, van Spil WE, Jansen MP, et al. Cohort profile: The Applied Public-Private Research enabling OsteoArthritis Clinical Headway (IMI-APPROACH) study: a 2-year, European, cohort study to describe, validate and predict phenotypes of osteoarthritis using clinical, imaging and biochemical markers. BMJ Open 2020;10(7):e035101.
41. Wirth W, Maschek S, Marijnissen ACA, et al. Test-retest precision and longitudinal cartilage thickness loss in the IMI-APPROACH cohort. Osteoarthritis Cartilage 2023;31(2):238–248.
42. Widera P, Welsing PMJ, Danso SO, et al. Development and validation of a machine learning-supported strategy of patient selection for osteoarthritis clinical trials: the IMI-APPROACH study. Osteoarthr Cartil Open 2023;5(4):100406.
43. van Helvoort EM, Jansen MP, Marijnissen ACA, et al. Predicted and actual 2-year structural and pain progression in the IMI-APPROACH knee osteoarthritis cohort. Rheumatology (Oxford) 2022;62(1): 147–157.
44. Hosmer DW Jr, Lemeshow S, Sturdivant RX. Applied Logistic Regression. John Wiley & Sons; 2013.
45. de Hond AAH, Steyerberg EW, van Calster B. Interpreting area under the receiver operating characteristic curve. Lancet Digit Health 2022; 4(12):e853–e855.
46. Huang Z, Chen J, Hu QS, et al. Meta-analysis of pain and function placebo responses in pharmacological osteoarthritis trials. Arthritis Res Ther 2019;21(1):173.
47. Englund M, Turkiewicz A. Pain in clinical trials for knee osteoarthritis: estimation of regression to the mean. Lancet Rheumatol 2023;5(6): e309–e311.
48. Vickers AJ, Kramer BS, Baker SG. Selecting patients for randomized trials: a systematic approach based on risk group. Trials 2006;7(1):30.
49. Wirth W, Ladel C, Maschek S, et al. Quantitative measurement of cartilage morphology in osteoarthritis: current knowledge and future directions. Skeletal Radiol 2023;52(11):2107–2122.