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SUMMARY

Objective: To investigate the test–retest precision and to report the longitudinal change in cartilage thickness, the percentage of knees with progression and the predictive value of the machine-learning-estimated structural progression score (s-score) for cartilage thickness loss in the IMI-APPROACH cohort – an exploratory, 5-center, 2-year prospective follow-up cohort.

Design: Quantitative cartilage morphology at baseline and at least one follow-up visit was available for 270 of the 297 IMI-APPROACH participants (78% females, age: 66.4 ± 7.1 years, body mass index (BMI): 28.1 ± 5.3 kg/m^2, 55% with radiographic knee osteoarthritis (OA)) from 1.5T or 3T MRI. Test–retest precision (root mean square coefficient of variation) was assessed from 34 participants. To define progressor knees, smallest detectable change (SDC) thresholds were computed from 11 participants with longitudinal test–retest scans. Binary logistic regression was used to evaluate the odds of progression in femorotibial cartilage thickness (threshold: −211 μm) for the quartile with the highest vs the quartile with the lowest s-scores.

Results: The test–retest precision was 69 μm for the entire femorotibial joint. Over 24 months, mean cartilage thickness loss in the entire femorotibial joint reached −174 μm (95% CI: [−207, −141] μm, 32.7% with progression). The s-score was not associated with 24-month progression rates by MRI (OR: 1.30, 95% CI: [0.52, 3.28]).

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Conclusion: IMI-APPROACH successfully enrolled participants with substantial cartilage thickness loss, although the machine-learning-estimated s-score was not observed to be predictive of cartilage thickness loss. IMI-APPROACH data will be used in subsequent analyses to evaluate the impact of clinical, imaging, biomechanical and biochemical biomarkers on cartilage thickness loss and to refine the machine-learning-based s-score.
Clinicaltrials.gov identification: NCT03883568.

Introduction

Clinical trials evaluating the efficacy of disease modifying osteoarthritis drug (DMOAD) candidates seek to enroll participants with high likelihood of structural progression and persistent pain over the course of the trial in order to demonstrate efficacy of the DMOAD candidates. Structural progression is, however, only observed in a minority of knee osteoarthritis (OA) patients[1]. In order to enrich clinical trial cohorts with knees likely to show structural progression, recent clinical trials used the presence of baseline radiographic joint space narrowing (JSN) as criterion[2,3]. Pain severity has been reported to be – on average – stable in knee OA patients enrolled in long-term observational studies over periods typically used for clinical trials[4–6]. Still, recent data suggested that OA patients may be more motivated to enroll in interventional trials when experiencing pain flares and a significant proportion of these OA patients therefore may show improvement that is not due to treatment intervention but due to regression to the mean[7,8]. The selection of knee OA patients based on data available at the time of enrollment therefore remains a challenge.

Recent studies reported machine-learning techniques to be capable of predicting symptomatic and/or structural OA progression[9–14] and such techniques may eventually provide reliable predictions of the subsequent development of symptomatic and structural OA status. In addition, machine-learning may allow to identify progression phenotypes[14], which could be of value for recruitment in future DMOAD trials as the efficacy of DMOADs may depend on OA phenotypes.

IMI-APPROACH (Applied Public-Private Research enabling OsteoArthritis Clinical Headway, https://www.approachproject.eu/, clinicaltrials.gov identifier: NCT03883568) is an exploratory, European, 5-center, 2-year prospective follow-up cohort project. IMI-APPROACH was designed to prospectively describe pre-identified progressor phenotypes with clinical and/or structural knee OA by use of conventional and novel clinical, imaging, and biochemical (bio)markers, and to validate and refine a predictive model for these (and new) progressor phenotypes based on these markers. The recruitment for IMI-APPROACH was based on rankings produced by machine-learning models that were trained using data from existing cohorts to estimate the likelihood of joint space width (JSW) loss (s-score) and/or increased or sustained knee pain (p-score) over the 24-month follow-up of the study from demographic data, pain assessments, and radiographic features with greater scores representing a greater probability of showing structural (s) or pain (p) progression (range: 0–1)[15]. As outcome measures for assessing structural progression, IMI-APPROACH relied on measurements of the radiographic JSW and MRI-based cartilage thickness loss. In order to provide study-specific precision error estimates and progression thresholds for MRI-based cartilage thickness measurements, IMI-APPROACH included a longitudinal MRI test–retest component.

The objectives of this study were:

a) to report the study-specific inter-site differences, the test–retest precision and the smallest detectable change (SDC) thresholds for cartilage thickness measurements in the IMI-APPROACH cohort,
b) to report the longitudinal change in quantitatively measured cartilage thickness over 6, 12, and 24 months and the percentage of knees showing cartilage thickness loss exceeding the SDC thresholds and
c) to investigate the association between the predicted structural progression probability (s-score) and observed 2-year cartilage thickness loss in the IMI-APPROACH cohort.

Materials and methods

Participants

IMI-APPROACH is an observational, longitudinal study that enrolled 297 OA patients with predominantly femorotibial OA at five clinical centers in Europe[16,17]. Recruitment relied on machine-learning models that were trained using data from the CHECK cohort to predict either the probability of increased or sustained knee pain or the probability of structural progression (defined as a reduction in JSW of $\geq$0.3 mm per year) over the next 2 years[15]. Participants from five existing observational OA cohorts (CHECK (Utrecht, The Netherlands)[18], HOSTAS (Leiden, The Netherlands)[19], MUST (Oslo, Norway)[20], PROCOAC (A Coruña, Spain)[21], and DIGICOD (Paris, France)[22]) or from outpatient departments, if not enough participants could be recruited from these existing cohorts, were invited for a screening visit. The trained machine-learning models were then applied to quantitative x-ray-based Knee Images Digital Analysis (KIDA) measures (e.g., JSW, osteophyte area)[23], which had the greatest importance for the structural progression model[15], and to demographic and clinical data collected at the screening visit to select OA patients with the highest likelihood of having pain and/or structural progression (approximately the highest 75% of combined p- and s-scores amongst the screened OA patients) over the course of the study[15]. The distribution of p- and s-scores for the included and excluded OA patients has been published[16,17]. No semi-quantitative Kellgren & Lawrence grades (KLG) or JSN scores were generated from the screening visit and hence a model could not be trained to use these. The knee clinically most severely affected from OA at the screening visit was selected as index knee based on opinion of physicians at the clinical sites; if both knees were affected equally, the right knee was selected. The index knee was required to have predominantly femorotibial OA and had to fulfill the clinical American College of Rheumatology (ACR) criteria[24]; a detailed description of the inclusion and exclusion criteria has been published[16]. Demographic and clinical data, blood and urine samples, and imaging data (weight-bearing X-ray,

MRI of the index knee) were collected from the participants at enrollment and at the month 6, 12, and 24 follow-up visits, CT images were collected at enrollment and 24 month follow-up only.

IMI-APPROACH was approved by the respective Institutional Review Boards (Netherlands: NL61405.041.17, Spain: 2015-651, France: 2017-A02469-44; Norway: 2017-1051) and was conducted in compliance with the study protocol, the Declaration of Helsinki, and the applicable ethical and legal regulatory requirements. All participants provided written informed consent.

Imaging

The MRI protocol included sagittal 3D spoiled or volume-interpolated gradient echo MRIs with selective water excitation or fat suppression for the quantitative cartilage analysis (Fig. 1). Two of the five centers used 1.5T scanners (A Coruña, Oslo), the other three centers used 3T scanners (Utrecht, Leiden, Paris, see Supplemental Table 1 for details). The slice thickness was 1.5 mm at all sites, the resolution was between 0.29 × 0.29 mm and 0.36 × 0.36 mm, the flip angle was 15° for 1.5T sites and 12° for 3T sites, the echo time ranged from 6.9 ms to 7.0 ms, and the repetition time was 17 ms (longer repetition times of up to 29 ms were used due to operator error in four of the scans).

Image assessments

The cartilage plates in the weight-bearing femorotibial joint were manually segmented from the MRIs by experienced readers with blinding to time point using custom software (Chondrometrics GmbH, Freilassing, Germany). All segmentations were quality-controlled by a single expert (S.M.) and corrections were performed as needed. The segmentations comprised the cartilage plates of the medial and lateral tibia (MT/LT) and of the central, weight-bearing medial and lateral femur (cMF/cLF, defined as 75% of the distance between the intercondylar notch and the posterior aspects of the femoral condyles, Fig. 1).

From the segmentations performed in the four femorotibial cartilage plates (MT, LT, cMF, cLF), the cartilage thickness (in mm) was computed for each of these. Cartilage thickness was further computed for 16 femorotibial subregions, each five in the MT and the LT, and each three in the cMF and the cLF, and for the central medial (cMFTC) and lateral (cLFTC) compartment, which were computed by subdividing the cartilage plates based on the shape of their subchondral bone area (Fig. 2)[25]. Finally, the cartilage thickness was computed for the combined measures medial and lateral femorotibial compartment (MFTC = MT + cMF, LFTC = LT + cLF), and entire femorotibial joint (FTJ = MFTC + LFTC). The longitudinal change in these location-based measures was computed for each of the observation periods (baseline → month 6, baseline → month 12, and baseline → month 24).

Location-independent measures of change in cartilage thickness allow to remove the link between the magnitude of change and the location of change and have been suggested to be more sensitive to between-group differences in change than location-based measures[26–28] and to be sensitive to structure-modifying interventions[29]. The current study included the cartilage thinning score (ThinningScore), which represents the sum of all negative changes observed in the femorotibial cartilage subregions within each knee, and the cartilage thickening score (ThickeningScore), which represents the sum of all positive changes observed in the femorotibial cartilage subregions within each knee[28].

Inter-site comparison, test–retest precision and smallest detectable change (SDC)

For the inter-site comparison, three volunteers had both knees imaged at four of the five sites. The images of each of these volunteers were processed as described above with reference to each other.

For the analysis of the test–retest precision, each site asked study participants at the baseline visit whether they volunteered into one additional MRI acquisition performed at both the baseline and the month 24 visit. Test–retest MRIs were acquired with repositioning of the knee between scans (patients were allowed but not required to leave the scanner) and were analyzed together with the other images from the respective participants as described above. In 14 of the 34 patients who agreed to test–retest acquisitions, the test–retest MRIs were acquired at the month 06 instead

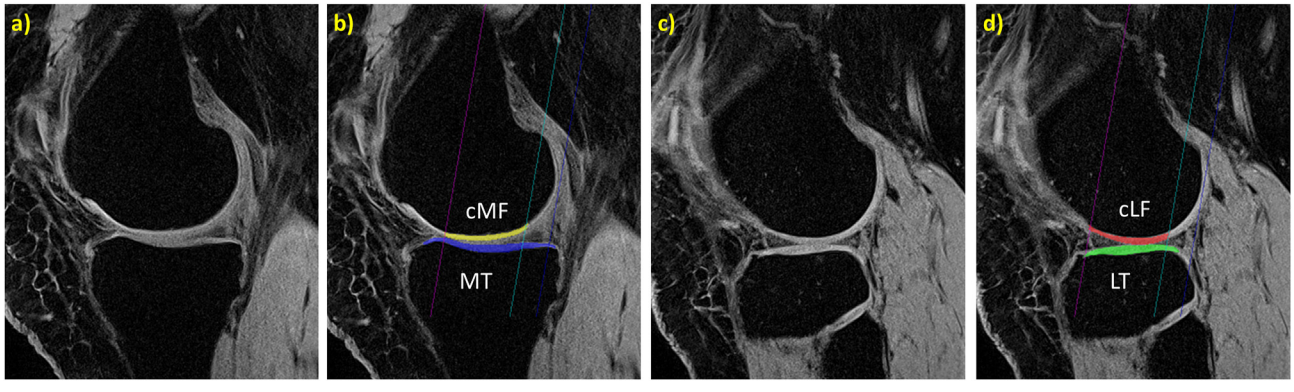

Fig. 1

Osteoarthritis and Cartilage

Illustration showing example scans of the medial (a) and the lateral femorotibial compartment (c) and the segmentation of the cartilages in the weight-bearing medial femorotibial compartment (b), MT: medial tibia, cMF: central, weight-bearing medial femur) and the weight-bearing lateral femorotibial compartment (d), LT: lateral tibia, cLF: central, weight-bearing lateral femur).

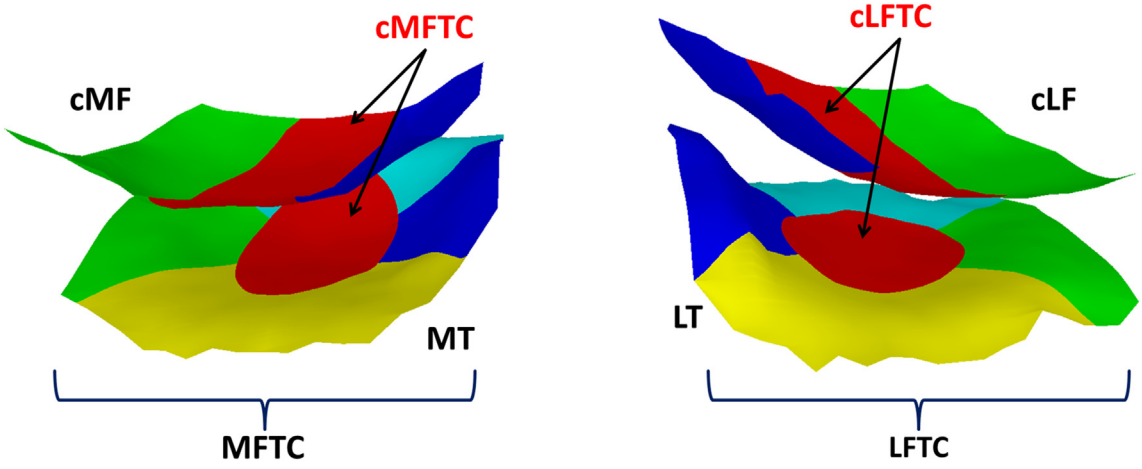

Fig. 2

Osteoarthritis and Cartilage

Illustration showing the cartilage subregions in the medial (MFTC) and the lateral (LFTC) femorotibial compartment. Each one central (red) and four peripheral subregions were defined in the medial (MT) and lateral (LT) tibia and each one central (red) and two peripheral subregions were defined in the central, weight-bearing medial (cMF) and lateral (cLF) femoral condyle. The central medial (cMFTC) and central lateral (cLFTC) femorotibial compartments are composed of the respective central cartilage subregions. External subregions are shown in green color, internal subregions are shown in blue color, anterior subregions are shown in turquoise color, and posterior subregions are shown in yellow color.

of the baseline visit, one center (A Coruña) acquired the second scan on a different day than the first scan (on average: 24 days later).

The smallest detectable change (SDC) threshold is based on the standard deviation (SD) of the differences in change observed in separate readings and allows to distinguish between knees with vs without progression (Appendix)[30]. For IMI-APPROACH, the SDC thresholds for change over 24 months were computed based on the measurements obtained from 11 participants that had test–retest data acquired at both the baseline and the month 24 visit.

Statistical analysis

The root-mean square (RMS) SD and coefficient of variation (CV %) were computed from baseline (or month 6) MRI to estimate the inter-site variability and the test–retest variability (Appendix).

Mean change, SD of the change, and 95% confidence intervals over the full 2-year observation period (baseline → month 24: $n = 226$ knees) and the intermediate observation periods (baseline → month 6: $n = 264$ knees, baseline → month 12: $n = 248$ knees) were reported for the various location-based and location-independent measures. The SDC thresholds computed from the longitudinal test–retest data were used to determine the percentage of knees exceeding the SDC thresholds for the different observation periods and measures.

The association between the predicted probability of structural progression (s-score) over the course of the study period and the observed 24-month structural progression exceeding the SDC threshold was analyzed using binary logistic regression with adjustment for site, age, sex, and body mass index (BMI) comparing the quartile with the highest s-scores against the quartile with the lowest s-scores in order to compare the knees with the highest vs the lowest progression probability. As comparator(s) for the s-score quartiles, these analyses were repeated using the presence of definite radiographic OA (ROA; KLG 2–4 vs KLG 0–1) as predictor. Progression in the entire FTJ was chosen as primary outcome measure, because IMI-APPROACH did not enroll participants with predominantly medial or lateral disease. The compartment-specific cartilage thickness measures (MFTC and LFTC) and the location-independent ThinningScore were selected as secondary outcome measures for these analyses. All analyses were performed using SPSS 27 (IBM Corporation, Armonk, NY).

Results

Of the 297 IMI-APPROACH participants, 270 had a baseline scan and at least one follow-up scan analyzed. The 210 women and 60 men were on average 66.4 ± 7.1 years old and had a BMI of 28.1 ± 5.3 kg/m^2 (Table I). A considerable proportion of the knees had no definite radiographic OA (45%, KLG 0/1: $n = 50/72$), but the majority (55%) of the knees had definite signs of radiographic OA (KLG 2/3/4: $n = 63/75/10$, Table I). Medial JSN was more frequent (46%) than lateral JSN (16%, Table I). The baseline cartilage thickness was 6.4 ± 1.1 mm for the entire FTJ, 3.0 ± 0.7 mm for the MFTC, and 3.4 ± 0.7 mm for the LFTC (Table I and Supplemental Table 2 for cartilage plates and subregions).

Inter-site comparison

One of the three volunteers had to be excluded from the inter-site comparison because of motion artifacts affecting both knees. For the remaining four knees from two participants, the cartilage thickness ranged from 6.41 ± 0.09 mm to 6.55 ± 0.12 mm in the entire FTJ, from 3.00 ± 0.07 mm to 3.11 ± 0.07 mm in the MFTC and from 3.40 ± 0.10 mm to 3.47 ± 0.10 mm in the LFTC (Supplemental Fig. 1). The RMS CV% was 1.9% for the entire FTJ (RMS SD: 120 μm), 2.6% for the MFTC (RMS SD: 79 μm) and 2.3% for the LFTC (RMS SD: 78 μm).

Test–retest precision

The test–retest precision (RMS CV%/SD) was 1.1%/69 μm for the entire FTJ, 1.4%/41 μm for the MFTC, and 1.3%/40 μm for the LFTC

		Mean/N	SD/%
Age	(years)	66.4	7.1
BMI	(kg/m^2)	28.1	5.3
Sex	Female	210	77.8
	Male	60	22.2
Side	Left	116	43.0
	Right	154	57.0
Site	A Coruna	39	14.4
	Leiden	47	17.4
	Oslo	29	10.7
	Paris	17	6.3
	Utrecht	138	51.1
KLG	0	50	18.5
	1	72	26.7
	2	63	23.3
	3	75	27.8
	4	10	3.7
Medial JSN	0	144	53.3
	1	69	25.6
	2	39	14.4
	3	15	5.6
lateral JSN	0	225	83.3
	1	23	8.5
	2	16	5.9
	3	3	1.1
Cartilage thickness	FTJ (mm)	6.4	1.1
	MFTC (mm)	3.0	0.7
	LFTC (mm)	3.4	0.7

SD: standard deviation, KLG: Kellgren & Lawrence grade, JSN: joint space narrowing, medial and lateral JSN grades were missing for $n = 3$ knees, FTJ: femorotibial joint, MFTC: medial femorotibial compartment, LFTC: lateral femorotibial compartment.

Table I Osteoarthritis and Cartilage

Demographic data of the 270 IMI-APPROACH participants that had MRIs from the baseline visit and at least one follow-up visit analyzed

(Table II). Results for cartilage plates are reported in Table II, results for cartilage subregions are shown in Supplemental Table 3.

The test–retest analysis revealed no obvious differences between sites that used 1.5T scanners and sites that used 3T scanners for the MRI acquisition; both the sites with the smallest (Utrecht) and the largest (Paris) precision errors used 3T MRI (Table II).

Longitudinal cartilage thickness change in the IMI-APPROACH cohort

In the whole cohort, the cartilage thickness loss in the entire FTJ was −49 ± 173 μm (95% CI: [−70, −28] μm) over the first 6 months, −91 ± 193 μm (95% CI: [−115, −67] μm) over the first 12

	All Sites ($n = 34$)		Paris* ($n = 7$)		Utrecht* ($n = 8$)		Leiden* ($n = 6$)		Oslo† ($n = 6$)		A Coruna† ($n = 7$)	
	RMS CV%	RMS SD	RMS CV%	RMS SD	RMS CV%	RMS SD	RMS CV%	RMS SD	RMS CV%	RMS SD	RMS CV%	RMS SD
FTJ	1.1	69	1.7	106	0.4	28	1.0	59	1.0	54	1.2	72
MFTC	1.4	41	2.2	64	0.5	15	1.0	27	1.4	40	1.4	44
LFTC	1.3	40	1.8	60	0.6	21	1.4	41	1.2	32	1.2	37
MT	1.5	22	2.3	32	1.1	16	1.5	21	1.4	19	1.1	17
cMF	2.0	29	2.5	38	0.9	13	2.4	34	1.8	26	2.0	30
LT	1.6	26	2.2	35	0.8	16	1.8	26	1.6	20	1.7	27
cLF	1.4	23	2.0	34	1.4	23	1.3	19	1.0	15	1.1	16

* 3T MRI.

† 1.5T MRI, RMS CV%: root mean square coefficient of variation (in %), RMS SD: root mean square standard deviation (in μm), FTJ: femorotibial joint, MFTC: medial femorotibial compartment, LFTC: lateral femorotibial compartment, MT: medial tibia, cMF: central medial femur, LT: lateral tibia, cLF: central lateral femur, test–retest MRI pairs were acquired at the baseline visit for 20 of the 34 knees, Paris/Utrecht/Oslo/A Coruna acquired $n = 1/2/6/5$ test–retest MRI pairs at month six instead of the baseline visit, all sites except for A Coruna acquired the test–retest MRI pairs on the same day.

Table II Osteoarthritis and Cartilage

Test–retest precision of cartilage thickness measurements across all sites and for individual sites

months, and reached −174 ± 250 μm (95% CI: [−207, −141] μm) over the entire 24 month observation period (Table III). Similarly, the magnitude of cartilage thickness loss in the MFTC, the LFTC, and the femorotibial cartilage plates increased with length of the observation period (Table III). Cartilage thickness loss was more pronounced in the MFTC than the LFTC over all observation periods, was greatest in the cMF, and smallest in the cLF (Table III).

The ThinningScore increased from −619 ± 437 μm (95% CI: [−672, −566] μm) over the first 6 months to −1040 ± 826 μm (95% CI: [−1148, −932] μm) over the entire 24 months, the ThickeningScore decreased from 411 ± 342 μm (95% CI: [370, 453] μm) over the first 6 months to 332 ± 282 μm (95% CI: [295, 369] μm) over the entire 24 months (Table III).

Within cartilage plates, the longitudinal cartilage thickness loss tended to be greater in the central than in the peripheral cartilage subregions and also increased with the length of the observation period (Supplemental Table 4).

Smallest detectable change (SDC) and progression in the IMI-APPROACH cohort

The SDC thresholds computed from 11 participants with longitudinal test–retest data at baseline and 24-months available were −211 μm for the entire FTJ, −120 μm for the MFTC, −125 μm for the LFTC, and −576 μm for the ThinningScore. When applied to the 24 months changes in cartilage thickness, the SDC thresholds resulted in 32.7% of the knees showing progression in the entire FTJ, 37.6% in the MFTC, 23.0% in the LFTC, and 69.0% in the ThinningScore (Table IV).

SDC thresholds and progression rates are reported in Table IV for cartilage plates and in Supplemental Table 5 for cartilage subregions.

Prediction of progression in the IMI-APPROACH cohort

The predicted probability of structural progression (s-score) was not associated with progression in the entire FTJ (OR: 1.30, 95% CI: [0.52, 3.28], %-progression in highest vs lowest quartile: 35.1% vs 22.8%): over 24 months (Table V). In knees from the quartile with the lowest s-score, a cartilage thickness loss of −144 ± 222 μm (95% CI: [−203, −85]) was observed, whereas in knees from the quartile with the highest s-score, the cartilage thickness loss amounted to −179 ± 253 μm (95% CI: [−246, −112], Table VI). Similarly, the s-score was not observed to be associated with progression in the MFTC, the LFTC, or the ThinningScore (Tables V and VI).

In comparison, the presence of ROA (i.e., KLG 2–4) was associated with 24-month progression in the entire FTJ (OR: 4.30, 95% CI: [2.23, 8.27], %-progression: 44.9% vs 19.4%) (Tables V and VI): and this was also reflected by the observed magnitude of change in knees with (−234 ± 281 μm, 95% CI: [−286, −183] μm) vs without ROA (−108 ± 193 μm, 95% CI: [−145, −71] μm, Table VI). The presence of ROA was also associated with progression in the MFTC, the LFTC, and the ThinningScore (Tables V and VI).

	SDC threshold	N progression	% progression
FTJ	<−211 μm	74	32.7
MFTC	<−120 μm	85	37.6
LFTC	<−125 μm	52	23.0
MT	<−54 μm	90	39.8
cMF	<−87 μm	65	28.8
LT	<−67 μm	63	27.9
cLF	<−83 μm	38	16.8
ThinningScore	<−576 μm	156	69.0

FTJ: femorotibial joint, MFTC: medial femorotibial compartment, LFTC: lateral femorotibial compartment, MT: medial tibia, cMF: central medial femur, LT: lateral tibia, cLF: central lateral femur, ThinningScore: location-independent cartilage thinning score.

Table IV

Osteoarthritis and Cartilage

Smallest detectable change (SDC) thresholds for 24 month change in cartilage thickness and 24 month progression rates

	BL → M06 (n = 264)				BL → M12 (n = 248)				BL → M24 (n = 226)			
	Mean	SD	95% CI		Mean	SD	95% CI		Mean	SD	95% CI	
FTJ	−49	173	−70	−28	−91	193	−115	−67	−174	250	−207	−141
MFTC	−38	109	−52	−25	−61	128	−77	−45	−103	151	−122	−83
LFTC	−11	95	−23	0	−30	103	−43	−17	−71	154	−92	−51
MT	−17	55	−24	−10	−29	65	−37	−21	−47	69	−56	−38
cMF	−21	68	−29	−13	−32	81	−42	−22	−56	100	−69	−43
LT	−12	52	−18	−5	−19	57	−26	−12	−41	78	−51	−30
cLF	1	59	−6	8	−11	65	−19	−3	−31	94	−43	−18
ThinningScore	−619	437	−672	−566	−769	564	−840	−699	−1040	826	−1148	−932
ThickeningScore	411	342	370	453	395	316	356	435	332	282	295	369

SD: standard deviation, 95% CI: 95% confidence intervals, FTJ: femorotibial joint, MFTC: medial femorotibial compartment, LFTC: lateral femorotibial compartment, MT: medial tibia, cMF: central medial femur, LT: lateral tibia, cLF: central lateral femur, ThinningScore: location-independent cartilage thinning score, ThickeningScore: location-independent cartilage thickening score.

Table III

Osteoarthritis and Cartilage

Longitudinal change in cartilage thickness (in μm) between the baseline (BL) and the month 6 (M06) follow-up visit, the BL and the month 12 (M12) follow-up visit, and between the BL and the month 24 (M24) follow-up visit

		OR	95% CI	
s-score	FTJ	1.30	0.52	3.28
	MFTC	1.35	0.56	3.24
	LFTC	1.71	0.63	4.70
	ThinningScore	1.49	0.61	3.68
Radiographic OA	FTJ	4.30	2.23	8.27
	MFTC	3.01	1.65	5.50
	LFTC	6.40	2.89	14.17
	ThinningScore	3.04	1.62	5.70

OR: odds ratio for highest vs lowest quartile (s-score) or presence vs absence (radiographic OA), 95% CI: 95% confidence intervals, FTJ: femorotibial joint, MFTC: medial femorotibial compartment, LFTC: lateral femorotibial compartment, ThinningScore: location-independent cartilage thinning score.

Table V Osteoarthritis and Cartilage

Association of the predictors predicted structural progression probability score (s-score) and presence of radiographic OA with 24 month cartilage thickness loss exceeding the smallest detectable change thresholds in $n = 226$ knees

Discussion

Our results show that the IMI-APPROACH project successfully enrolled participants that exhibited substantial longitudinal cartilage thickness loss, although the predicted structural progression probability score (s-score) used for enrollment of participants was not observed to be associated with subsequent cartilage thickness loss. Instead, the presence of radiographic OA, which was included as a comparator to the s-score, was observed to be a strong predictor of cartilage thickness loss over the 24 months observation period. In addition, we could demonstrate a high test–retest precision for this multi-center study and provided SDC-thresholds that allow distinguishing between knees with vs without progression.

The test–retest precision errors observed in the current study were rather low when compared to data from a previous observational multi-center study comparing the precision of both 1.5T and 3T MRI[31] or a recent clinical trial, which used a comparable MRI protocol as IMI-APPROACH[32]. Interestingly, the test–retest precision errors were not observed to be greater for the site that acquired the test–retest scans on different days when compared to the other sites. Despite the lower signal-to-noise ratio of 1.5T MRI, the precision errors were also not higher for 1.5T MRI than for 3T MRI in the current study, which allowed pooling the longitudinal test–retest data for computing one global SDC threshold for the IMI-APPROACH cohort. The inter-site variability exceeded the intra-site variability in this study. This may be explained by the dependency of the morphometric analyses on the characteristics of the individual scanning equipment but also by the small sample size of the inter-site analysis.

About one third of the knees that had 24-month follow-up data were observed to show progression exceeding the SDC thresholds in the entire FTJ. This progression rate and the associated magnitude of quantitative cartilage thickness loss observed in this study over 2 years are comparable to the magnitude of change and the progression rates previously observed in a cohort of 441 knees with KLG 2 or 3 from the Osteoarthritis Initiative (OAI) over comparable intervals[33] and will allow utilizing the data from the IMI-APPROACH cohort to study the structural progression in different OA phenotypes in future analyses with the possibility to cross-validate findings with data from the OAI. On a compartment-level, the progressor rates were higher for the medial than the lateral compartment, which can be explained by the greater number of knees with medial than lateral JSN, because JSN has been shown to predict cartilage thickness loss in the narrowed compartment[34]. Cartilage thickness loss was, however, not only observed in knees with established ROA in the current study, but also in knees without definite signs of ROA, which typically show no or only little cartilage thickness loss[35] and which are typically not considered for inclusion in clinical trials. The wealth of data collected as part of the IMI-APPROACH project may allow to identify risk factors associated with progression in these pre-ROA knees in future analyses.

The machine-learning-based s-score, which was used for enrollment of participants in the IMI-APPROACH project, has been observed to be (to some degree) predictive of minimum JSW loss[36], but was not observed to be predictive of subsequent cartilage thickness loss in this study, even though only the quartile with the highest predicted progression probability was compared against the quartile with the lowest progression probability. This score was trained using data from observational cohorts to predict loss in minimum JSW, and high baseline JSW was one of the factors associated with subsequent JSW loss during training of this score. This is in contradiction to previous observational studies, which reported narrowing of the joint space to be predictive of MRI-based cartilage thickness loss[34,37–39], and to the practice in recent clinical trials, which utilized the presence of JSN to enrich the cohort with knees likely to show structural progression[2,3]. The discrepancy may be explained by the use of the same baseline radiograph for both predicting subsequent change and measuring the outcome (JSW loss) for training the machine-learning model: An overestimation of the real baseline JSW due to precision error will lead to a greater observed JSW loss when using the same baseline radiograph both for prediction and as reference for measuring change, while an underestimation of the real baseline JSW due to precision error will lead to a smaller observed JSW loss. Depending on the magnitude of the precision error and the magnitude of real JSW loss, the use of the same baseline radiograph may have biased the machine-learning model towards precision-error-related observed JSW loss instead of real JSW loss. Given that the machine-learning model was trained using a cohort that included a large proportion of knees without OA or with early OA (CHECK), in which change induced by precision errors may have outweighed the real JSW change, this effect may have had a particular impact on the predicted structural progression probability score. In addition, JSW and MRI progression were only weakly correlated in the IMI-APPROACH cohort[40]. Hence it is not surprising that the s-score, defined to predict JSW-based progression, was not predictive of MRI-based progression in the current study. Refinement of the machine-learning model based on these observations and potentially a machine-learning model trained for specifically predicting MRI-based cartilage thickness loss will offer the possibility to apply the model to other cohorts in the future. Such a tailored model may potentially provide superior predictions compared to radiographic evaluation, which was found to be highly predictive of structural progression in the current study.

A limitation of this study is that the machine-learning model used for the prediction of progression was trained on historical data from CHECK cohort participants and that some of these CHECK cohort participants were later screened for inclusion into IMI-APPROACH. The data set, from which the progression probability was predicted, was therefore not fully independent from the data set used for training the models. Still, the characteristics of the CHECK cohort participants used for training and prediction (e.g., radiographic measures, demographic data, pain severity and

	Cartilage thickness change				Progression		Cartilage thickness change				Progression	
	Mean	SD	95% CI		N	%	Mean	SD	95% CI		N	%
	Lowest s-score quartile ($n = 57$)						Highest s-score quartile ($n = 57$)					
FTJ	−144	222	−203	−85	13	22.8	−179	253	−246	−112	20	35.1
MFTC	−98	157	−140	−56	18	31.6	−84	129	−118	−49	22	38.6
LFTC	−46	93	−71	−21	9	15.8	−95	185	−144	−46	18	31.6
ThinningScore	−902	708	−1090	−714	36	63.2	−1104	828	−1324	−885	42	73.7
	No Radiographic OA ($n = 108$)						**Radiographic OA ($n = 118$)**					
FTJ	−108	193	−145	−71	21	19.4	−234	281	−286	−183	53	44.9
MFTC	−70	121	−93	−47	29	26.9	−133	169	−164	−102	56	47.5
LFTC	−38	129	−63	−14	10	9.3	−101	169	−132	−71	42	35.6
ThinningScore	−800	635	−921	−678	63	58.3	−1260	917	−1427	−1093	93	78.8

SD: standard deviation, 95% CI: CI: 95% confidence intervals, FTJ: femorotibial joint, MFTC: medial femorotibial compartment, LFTC: lateral femorotibial compartment, ThinningScore: location-independent cartilage thinning score.

Table VI

Osteoarthritis and Cartilage

24-month cartilage thickness loss (in μm) stratified by the predictors predicted structural progression probability score (s-score) and presence of radiographic OA in $n = 226$ knees

location) changed between the data collection performed as part of the CHECK study and the screening visit of IMI-APPROACH (5–16 years later), making a bias unlikely. Another limitation of the current study is that only about one third of the participants planned to have test–retest MRIs acquired at baseline and 24 months follow-up actually had test–retest MRIs acquired at these visits and that the SDC thresholds could therefore only be computed using data from three of the five centers. Still, the number of participants with longitudinal test–retest data was in the same range as the number of participants from the OAI pilot study that were previously used for computing SDC thresholds[41,42]. Another potential limitation of the study is that the SDC thresholds depend on the length of the observation period and that the number of knees with progression was therefore only determined for the full (2-year) observation period and not for the intermediate observation periods. SDC thresholds for a 1-year observation period have, however, been previously reported based on data from the OAI pilot study[41,42]. Another limitation is that the analysis comprised the weight-bearing femorotibial joint only and did not include the patellofemoral joint or the posterior aspects of the femoral condyles. The analyzed region was chosen because of the focus on femorotibial OA in IMI-APPROACH and to match the region of interest analyzed in clinical trials[3,43]. It also is the only region for which eligibility assessments are possible from standing, weight-bearing radiographs. Finally, the inter-site analysis included only few knees. For this reason, this study was not able to investigate the impact of site- or scanner-specific factors on the observed cartilage thickness measurements.

In conclusion, IMI-APPROACH successfully enrolled participants with substantial cartilage thickness loss and a considerable proportion of knees with structural progression exceeding the SDC thresholds over the 24-month observation period. These data will be used in subsequent analyses to evaluate the impact of the numerous clinical, imaging, biomechanical and biochemical biomarkers on cartilage thickness loss and will also be used to refine the machine-learning model-based structural progression probability score, which was not observed to be associated with cartilage thickness loss in the current study.

Author contributions

Study conception and design: WW, ACAM, AL, FJB, FB, MK, IKH, CHL, JB, FE, FWR, FPJGL, HHW, MJ.

Acquisition of data: All authors.

Analysis & interpretation of data: WW, MJ.

Writing of first manuscript draft: WW, MJ.

Critical manuscript revision and approval of final manuscript: All authors.

WW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of competing interest

•Wolfgang Wirth: Employee and shareholder of Chondrometrics GmbH and consulting fees from Galapagos NV.

•Susanne Maschek: Employee and shareholder of Chondrometrics GmbH.

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Appendix

The SDC was calculated according to Bruynesteyn *et al.*[30]: SDC = $1.96*\frac{SD_{DC}}{\sqrt{2}}$, with SD_{DC} representing the SD across the differences of the changes observed in the test and the retest readings.

The RMS standard deviation (RMS SD) and the RMS coefficient of variation (RMS CV%) were calculated according to Gluer *et al.*[44]: RMS SD= $\sqrt{\sum_{j=1}^{m}\frac{SD_j^2}{m}}$, with m the number of knees; RMS CV % = $\frac{\text{RMS SD}}{\sum_{j=1}^{m}\frac{\overline{x_j}}{m}}*100\%$, with m the number of knees and with $\overline{x_j}$ the mean across observations in knee j.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2022.10.015.

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