Cartilage Topography Assessment With Local-Area Cartilage Segmentation for Knee Magnetic Resonance Imaging

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Objective. Local-area cartilage segmentation (LACS) software was developed to segment medial femur (MF) cartilage on magnetic resonance imaging (MRI). Our objectives were 1) to extend LACS to the lateral femur (LF), medial tibia (MT), and lateral tibia (LT), 2) to compare LACS to an established manual segmentation method, and 3) to visualize cartilage responsiveness over each cartilage plate.

Methods. Osteoarthritis Initiative participants with symptomatic knee osteoarthritis (OA) were selected, including knees selected at random (n = 40) and knees identified with loss of cartilage based on manual segmentation (Chondrometrics GmbH), an enriched sample of 126 knees. LACS was used to segment cartilage in the MF, LF, MT, and LT on sagittal 3D double-echo steady-state MRI scans at baseline and at 2-year follow-up. We compared LACS and Chondrometrics average thickness measures by estimating the correlation in each cartilage plate and estimating the standardized response mean (SRM) for 2-year cartilage change. We illustrated cartilage loss topographically with SRM heatmaps.

Results. The estimated correlation between LACS and Chondrometrics measures was \( r = 0.91 \) (95% confidence interval [95% CI] 0.86, 0.94) for LF, \( r = 0.93 \) (95% CI 0.89, 0.95) for MF, \( r = 0.97 \) (95% CI 0.96, 0.98) for LT, and \( r = 0.87 \) (95% CI 0.81, 0.91) for MT. Estimated SRMs for LACS and Chondrometrics measures were similar in the random sample, and SRM heatmaps identified subregions of LACS-measured cartilage loss.

Conclusion. LACS cartilage thickness measurement in the MF and LF and tibia correlated well with established manual segmentation–based measurement, with similar responsiveness to change, among knees with symptomatic knee OA. LACS measurement of cartilage plate topography enables spatiotemporal analysis of cartilage loss in future knee OA studies.

INTRODUCTION

Cartilage measurement on magnetic resonance imaging (MRI) provides a relevant structural outcome for osteoarthritis (OA) studies (1,2). Accurate and reliable measurement of structural change should facilitate high-quality clinical trials of OA therapies, with improved assessment of disease development and progression. Longitudinal observational studies of knee OA, such as the Osteoarthritis Initiative (OAI) (3,4), have collected thousands of knee MRI data sets with the potential for investigation of cartilage and other structural features as outcomes. However, due to cost and resource limitations, only limited subsets of the available MRI scans have been read for cartilage volume. Therefore, a need exists for an accurate, objective, reliable, and fast method for cartilage volume measurement.

A conventional clinical MRI reading, while offering a comprehensive assessment of knee OA, makes no attempt to quantify structural damage due to disease. For research purposes, several semiquantitative scoring systems have been developed (5–7), but these are based on qualitative and subjective assessments that...
SIGNIFICANCE & INNOVATIONS

- The semiautomated and updated local-area cartilage segmentation (LACS) software allows for fast, reproducible, responsive, and valid quantification of cartilage change (volume or thickness) on magnetic resonance imaging in multiple areas of the femorotibial joint. The underlying coordinate system is computer-driven and based on anatomical landmarks, which allows for consistent measurements between repeated scans, such as in longitudinal studies and in clinical trials.
- We present a novel method to visualize change in cartilage topography through heatmaps.
- The updated LACS method may find application in future clinical osteoarthritis trials to monitor treatment response and potentially guide management decisions in patient care.

MATERIALS AND METHODS

Study design, setting, and participants. The OAI is a multicenter, observational, longitudinal cohort study, with publicly available protocols and data releases (https://nda.nih.gov/oai/). Individuals with or at risk for symptomatic knee OA, ages 45–79 years, were recruited between 2004 and 2006 from the University of Maryland School of Medicine and Johns Hopkins University (Baltimore, MD), Ohio State University (Columbus, OH), University of Pittsburgh (Pittsburgh, PA), and Memorial Hospital of Rhode Island (Pawtucket, RI); the OAI Coordinating Center was located at the University of California, San Francisco (UCSF). The institutional review board at each recruitment site and at UCSF approved the study, and all participants gave informed consent.

The OAI Progression cohort participants had symptomatic knee OA in at least 1 knee at baseline, defined as a definite osteophyte (Osteoarthritis Research Society International [OARSI] atlas grade 1–3, based on clinical center radiographic screening at baseline) and frequent knee symptoms. Knees in the core image assessment sample were selected from the progression cohort based on availability of fixed-flexion knee radiographs and MRI scans from both the baseline and 24-month clinic visits; measurements of cartilage thickness from manually segmented MRIs are publicly available (Chondrometrics GmbH; Project 9B; https://nda.nih.gov/oai/full_downloads.html). We drew a random sample of 40 knees, as well as 25 knees above the upper quartile of 2-year cartilage thickness loss for each of 4 cartilage plates, based on Chondrometrics GmbH ThCcAB measurements (mean thickness of the cartilage over total area of subchondral bone covered with cartilage, which are highly correlated with ThCcAB [mean thickness of the cartilage over total area of subchondral bone] measurements). Since some knees were both randomly selected and selected for loss, and/or selected for loss in >1 cartilage plate, the total number of unilateral knees identified for segmentation was 126 (not 140).

Radiograph acquisition and interpretation and MRI acquisition. Bilateral posteroanterior fixed-flexion weight-bearing radiographic views were obtained using a SynaFlexer frame (Synarc). The detailed radiographic procedure manual is available online (https://nda.nih.gov/oai/). Briefly, 2 expert central readers assessed the images using the Kellgren/Lawrence (K/L) and OARSI atlas criteria, and discrepancies were adjudicated in a consensus session or otherwise decided by the senior reader, an experienced musculoskeletal radiologist. MRI scans were acquired at OAI clinical centers using identical dedicated Siemens Trio 3T scanners using the sagittal double-echo steady-state (DESS) 3D MRI scans (sagittal, 0.365 mm × 0.365 mm, 0.7-mm slice thickness, repetition time 16.5 msec, echo time 4.7 msec).

LACS. Using the LACS semiautomated software, cartilage volume and average thickness (volume normalized to surface area) was segmented in the 4 weight-bearing regions (LF, MF, LT, and MT) in 126 participants. The only manual steps are described in Figure 1, and reader time was estimated to be approximately 10 minutes per cartilage plate.

Similar to the MF segmentation (20), the LACS LF cartilage segmentation is based on a cylindrical coordinate system,
defined in 3D space by 3 variables: \( r, \theta, \) and \( z \) (Figure 2A) (18). The \( \theta \) variable is the rotation on the sagittal axis, radiating from the \( z \) axis. The \( z \) variable relates to the location in the medial-lateral direction, from a value of \( z = 0.0 \) at the outer edge of the lateral femoral condyle to \( z = 1.0 \) at the most medial location of the femoral condyle, identified by a reader. The \( z \) axis is defined to pass through the center of a circle that was fit to the bone margins at the center of each condyle. Since the \( r \) variable is roughly perpendicular to the cartilage surface, it is not used for our analysis. For future methodologies, \( r \) could potentially be used to characterize changes in bone shape. The segmented femur cartilage region was defined from \( \theta = 165^\circ \) to \( 255^\circ \) for both compartments and with a range in \( z \) from 0.71 to 0.89 in the medial compartment and 0.16 to 0.30 in the lateral compartment.

The tibia cartilage segmentation is based on a warped 2D Cartesian coordinate system defined by 2 dimensionless variables: \( x \) and \( y \) (Figure 2B). The \( x \) variable relates to the location in the lateral-medial direction, from a value of \( x = 0.0 \) at the outer edge of the LT to \( x = 1.0 \) at the most medial location of the MT, indicated by a reader. The range of \( x \) is from 0.71 to 0.89 in the medial compartment and 0.15 to 0.31 in the lateral compartment. The \( y \) variable relates to the length of the tibia plateau in a sagittal plane, following the bone contour in an anteroposterior direction from a value of \( y = 0.0 \) at the anterior edge to \( y = 1.0 \) at the posterior edge of the tibia, indicated by a reader. The landmarks generally produce a trapezoid-shaped measurement region, since the cartilage plate is wider (in the sagittal plane) for more central regions. To maintain consistency and simplify the surface area calculations, we defined a warped coordinate system with the origin \((x = 0, y = 0)\) at 1 corner and the location \((x = 1, y = 1)\) at the opposite corner of the trapezoid.

The flexible nature of the software allows for post hoc adjustment of measurement regions within the fully segmented cartilage plates by relocating \( \theta, z, x, \) and/or \( y \) depending on the desired analyses. For reproducibility, we measured the entire segmented cartilage except a minor frame trim to eliminate uneven edges. For responsiveness and correlation, we limited the measurement area to the central weight-bearing region of the tibiofemoral joint, similar to the regions measured by Chondrometrics. However, spatial boundaries from LACS will not be identical to those from Chondrometrics. For the specific frame trims, see Supplementary Figure 1, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002acr.24745.

**Cartilage topography assessment and reliability.** The flexible nature of LACS permits cartilage to be measured with granularity within the cartilage plate, through a grid that can be defined within a region by picking specific \( \theta, z, x, \) and/or \( y \) values and increments over the measurement region, and is consistent across multiple time points. To illustrate the potential utility of this approach, we present 2-year change in cartilage volume as SRM heatmaps, with visual representations of responsiveness over the measurement region. For intra- and interreader reliability of the manual steps of the semiautomated cartilage segmentation, the 4 cartilage plates in 20 baseline scans, randomly selected from the
126 segmented knees, were re-segmented by the experienced reader (AM) and a trained medical student (EH) ≥2 weeks after the initial segmentation.

**Statistical methods.** Baseline radiographic knee OA status was summarized for each sample, including K/L grade and OARSI joint space narrowing grades in the medial and lateral compartments, with the number of knees and percent in each grade. The LACS cartilage volume and average thickness distributions were summarized with mean ± SD and quartiles for each sample.

We compared LACS average cartilage thickness measurements with cartilage thickness measurements in central subregions (ThCtAB: center of central lateral femur, center of central medial femur, central lateral tibia, and central medial tibia) from the released OAI readings by Chondrometrics, since they were reported as the most responsive regions among Chondrometrics assessments (21). LACS delineates subregions with unique coordinate systems not used by the Chondrometrics method. Measurements obtained using the Chondrometrics method cannot be considered a perfect gold standard for comparison to LACS, since

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**Figure 2.** Local-area cartilage segmentation (LACS) coordinate-derived segmented cartilage (blue) in femur and tibia. **A,** In the femur, a cylindrical coordinate system defines locations in 3D space by 3 variables: r, θ, and z. **B,** In the tibia, a 2-axis coordinate system defines locations in 2D space by 2 variables: x and y.
subregion delineation is method-specific and therefore not interchangeable. We sought to establish concurrent validity of LACS based on correlation with manual segmentation, due to potential differences in subregional boundaries. We generated scatterplots of LACS versus Chondrometrics cartilage thickness and estimated Pearson’s and Spearman’s correlations between LACS volume and Chondrometrics cartilage thickness in the collective sample of 126 knees, including a baseline and 2-year follow-up measurement for each knee. Bias-corrected and acceleration-adjusted (BCa) bootstrap 95% confidence intervals (95% CIs) for correlation coefficients were based on 20,000 replicates, with the bootstrap sample size equal to the number of knees. We also generated Bland-Altman plots of the difference between the measurements against their mean, including limits of agreement (22), with some lack of agreement expected given differences in the delineation of subregional boundaries.

We compared responsiveness of LACS and Chondrometrics cartilage volume and thickness measurement in similar central subregions over 2 years in the random sample of knees (n = 40) by estimating the standardized response mean (SRM = mean [Δ]/SD[Δ]) for the 2 methods, and the difference in SRM between methods. Then in knees selected for loss of cartilage thickness in each of the 4 cartilage plates (25 knees in each plate with 2-year loss above the highest quartile) as measured by Chondrometrics, we estimated SRM for LACS volume and thickness measurements. BCa bootstrap 95% CIs for SRM were based on 20,000 replicates.

Since LACS measures volume over a grid of the cartilage plate, we were able to estimate SRM over the grid of each cartilage plate.
Figure 4. Bland-Altman plots of the differences between local-area cartilage segmentation (LACS) and Chondrometrics measurements. See Figure 3 for abbreviations.
plate in the random sample of knees, as well as knees selected for loss of Chondrometrics cartilage thickness, and we displayed the results in the form of responsiveness heatmaps, with darker regions reflecting greater responsiveness. Figures were generated with R package ggplot2 (23).

We evaluated intra- and interreader reliability of the LACS method in a limited sample of 20 knees randomly selected from the 126 knees, in which the experienced reader repeated the measurements for each cartilage plate in each knee, and a trained medical student segmented each cartilage plate once in the same 20 knees. The intra- and interreader reliability was evaluated by estimating interclass correlation coefficients (ICCs) from a linear mixed model for each cartilage plate, with a fixed effect for reader and random effects for knee and reader within knees. BCa bootstrap 95% CIs for the ICCs were based on 20,000 replicates, with resampling at the knee level. Since ICCs are unitless and difficult to interpret, we also evaluated absolute measurement differences for both volume and thickness. We estimated the mean absolute intrareader difference, defined as the mean difference between any 2 measurements on the same knee from the same reader, as well as the mean absolute interreader difference, defined as the mean difference between any 2 measurements on the same knee from different readers; 95% CIs were based on percentiles of 20,000 bootstrap replicates (24,25).

### RESULTS

**Sample description.** Participants included non-Hispanic White patients (n = 97, 77%), African Americans (n = 23, 18%), and other ethnic/racial groups (n = 6, 5%), with 52% women and a mean ± SD age of 62 ± 9 years, and mean ± SD body mass index of 30 ± 5.2 kg/m². Most of the knees had mild to moderate OA based on centrally read radiographs (35% K/L grade 2, 60% K/L grade 3), with joint space narrowing more common in the medial compartment (see Supplementary Table 1, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24745). In knees identified with excessive cartilage loss over 2 years (i.e., loss above the highest quartile measured by Chondrometrics), LACS demonstrated a significant loss of cartilage volume and thickness.

### Concurrent validity.** LACS and Chondrometrics cartilage thickness measurements are shown in scatterplots for the collective sample (n = 126), including measurements from baseline and 2-year follow-up, for each cartilage plate (Figure 3). Estimated Pearson’s correlation between LACS and Chondrometrics thickness measures was \( r = 0.91 \) (95% CI 0.86, 0.94) for LF, \( r = 0.93 \) (95% CI 0.89, 0.95) for MF, \( r = 0.97 \) (95% CI 0.96, 0.98) for LT, and \( r = 0.87 \) (95% CI 0.81, 0.91) for MT. Estimated Spearman’s correlation coefficients were similar to Pearson’s estimates (data not shown). Bland-Altman plots of the differences between LACS and Chondrometrics measurements versus their means show minimal evidence of a relationship between measurement error and the true value, with estimated limits of agreement (Figure 4). Observed biases in the Bland-Altman plots may also suggest spatial nonuniformities in cartilage thickness in each of the plates. Given that LACS and Chondrometrics probe somewhat different portions of the central area of each plate, a uniformly thick plate should show no bias in the plots, while variations in thickness will produce biases.

**Responsiveness.** In a random sample of knees (n = 40), the SRM estimates for 2-year change in LACS and Chondrometrics cartilage volume and thickness were similar, with the limits of the 95% CIs for the differences in SRM ranging from negative differences (LACS more responsive) to positive differences (Chondrometrics more responsive); thus the data were compatible with potentially modest or no difference in responsiveness between the 2 methods in a population of knees with symptomatic knee OA (Table 1).

### Table 1. Responsiveness of LACS and Chondrometrics cartilage measurements: 2-year change in a random sample of knees (n = 40)*

| Cartilage plate | LACS | Chondrometrics |
|-----------------|-----|----------------|
| Volume, mm³     |     |                |
| Lateral femur   | -9.3 ± 60.8 | -0.15 (-0.43, 0.18) | cLF.VC | -19.9 ± 86.2 | -0.23 (-0.50, 0.08) | 0.08 (-0.24, 0.43) |
| Medial femur    | -46.4 ± 102.4 | -0.45 (-0.69, -0.16) | cMF.VC | -55.0 ± 149.4 | -0.37 (-0.63, -0.03) | -0.08 (-0.38, 0.11) |
| Lateral tibia   | -22.2 ± 57.8 | -0.38 (-0.71, -0.02) | LT.VC | -30.1 ± 102.9 | -0.29 (-0.57, 0.04) | -0.09 (-0.42, 0.20) |
| Medial tibia    | -27.6 ± 88.4 | -0.31 (-0.58, -0.01) | MT.VC | -37.4 ± 120.1 | -0.31 (-0.60, 0.01) | 0.00 (-0.39, 0.37) |

| Thickness, mm   |     |                |
| Lateral femur   | -0.07 ± 0.19 | -0.35 (-0.60, -0.04) | cLF.ThCtAB | -0.02 ± 0.12 | -0.13 (-0.43, 0.20) | -0.22 (-0.55, 0.08) |
| Medial femur    | -0.12 ± 0.28 | -0.41 (-0.62, -0.14) | cMF.ThCtAB | -0.15 ± 0.28 | -0.52 (-0.77, -0.25) | 0.11 (-0.07, 0.30) |
| Lateral tibia   | -0.09 ± 0.14 | -0.64 (-0.90, -0.34) | cLT.ThCtAB | -0.08 ± 0.14 | -0.59 (-0.89, -0.30) | -0.04 (-0.39, 0.30) |
| Medial tibia    | -0.06 ± 0.16 | -0.34 (-0.61, -0.02) | cMT.ThCtAB | -0.08 ± 0.17 | -0.47 (-0.76, -0.13) | 0.13 (-0.27, 0.51) |

* 95% CI = 95% confidence interval; c (i.e., cLT) = central; cc = center of central; LACS = local-area cartilage segmentation; LF = lateral femur; LT = lateral tibia; MF = medial femur; MT = medial tibia; SRM = standardized response mean; ThCtAB = mean thickness of the cartilage over total area of subchondral bone; VC = volume of cartilage.
based on the estimated SRMs and 95% CIs (see Supplementary Table 3, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24745).

LACS SRM heatmaps, with darker regions representing greater responsiveness, also reflect loss of cartilage. The heatmaps identified subregions of cartilage loss in the random sample of knees and knees identified with 2-year loss measured by Chondrometrics (Figure 5). As expected, the latter visualized greater change. In this sample, the tibia plateaus had greater responsiveness centrally, whereas responsiveness in the femur condyles was skewed somewhat anteriorly toward the most weight-bearing areas (perpendicular to the femur shaft).

Reliability. In the LF, MF, and LT, the estimated ICCs for intra- and interreader reliability were close to 1, with lower bounds of the 95% CIs of $\geq 0.9$. In the MT, the ICC for intrareader reliability of volume was 0.91 (95% CI 0.71, 0.94), and for interreader reliability it was 0.90 (95% CI 0.78, 0.97). The estimated mean absolute interreader difference was greatest in the MT, 92 mm$^3$ (95% CI 62, 125), and as small as 45 mm$^3$ (95% CI 37, 53) for the LT (see Supplementary Table 4, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24745).

DISCUSSION

The semiautomated LACS software for knee cartilage segmentation was extended from the medial femur to other cartilage plates, including the LF, MT, and LT. LACS cartilage measures correlated well with cartilage measures from an established manual segmentation method, with similar responsiveness to change, and excellent reliability, among knees with symptomatic knee OA. We also used SRM heatmaps to visualize cartilage volume responsiveness over a grid of the cartilage plate and identified subregions of LACS-measured cartilage loss.

The LACS coordinate system is based on anatomical bony landmarks and permits measurement within any subregion of

Figure 5. Local-area cartilage segmentation standardized response mean (SRM) heatmaps; A, Lateral femur; B, Medial femur; C, Lateral tibia; D, Medial tibia; randomly selected knees (left panels), and knees selected for 2-year loss by Chondrometrics measures (right panels). Darker regions represent greater responsiveness over 2 years.
the femorotibial joint consistently across longitudinal assessments. The researcher chooses the measurement area (i.e., area of interest) after full-compartment segmentation. For the purpose of comparison and validation, we assessed areas that corresponded with Chondrometrics subregions (26). Therefore, we did not attempt to identify and restrict measurements to subregions with greater potential for responsiveness. While it has previously been suggested that shrinking the measurement region around a center point \( z_0 \) and \( \theta_0 \) in the medial femur does not improve responsiveness (18), our SRM heatmaps illustrate that identifying subregions of greater responsiveness may be possible. Another approach may be to center unique index points for areas of maximum thinning in each patient and follow areas longitudinally, which has demonstrated superior responsiveness to change (20). The heatmaps also allow for pattern comparison, e.g., in relation to biomechanical risk factors such as knees with different alignment.

High-quality assessment of disease progression, including accurate and reliable measurement of structural change, is critical to the evaluation of potential OA therapies in randomized trials. One study proposed to extract topographic measurements from MRI to create cross-sectional cartilage thickness maps (11). LACS offers measurement and visualization of cartilage plate “topography,” including changes from baseline to follow-up. Measuring volume over a grid of the cartilage plate longitudinally may allow for spatiotemporal modeling, incorporating individual differences in the temporal evolution of OA in affected subregions (27). The granularity seen on the heatmaps offers substantially more information than radiographic fixed location joint space width, which is a 2D measurement and varies much more gradually as a function of measurement location (28). We anticipate that the shape of the heatmap surface could be parameterized to offer a more nuanced assessment of change in cartilage plate volume and thickness. These possibilities remain to be explored in a future study with a larger sample size.

The semiautomated approach requires minimal initiation and interaction by the user. Our efforts to decrease MRI reader time while maintaining performance directly address the high cost of processing a large quantity of MRIs. Segmenting cartilage manually is straightforward but is also resource intensive and subject to reader bias and error. Semiquantitative and quantitative measurements of cartilage from 3T MRIs have been applied in several studies (29–31), although the advantage of MRI is offset by the substantial reader time required to evaluate and/or segment cartilage plates on numerous tomographic images. For example, each annual OAI visit involves several MRI sequences for each knee, and the sequence for cartilage alone (DESS) has an average of 160 slices per knee. Our extended method leverages the unique resources of existing large OA observational cohorts with an abundance of longitudinal high-resolution 3T MRIs and patient-reported outcome measures. Our future goal is to apply the LACS method to all MRIs in the OAI and make the data publicly available.

LACS correlated well with an established manual segmentation method, with similar responsiveness to change and excellent reliability. Bowes et al recently reported accurate and repeatable measures of cartilage thickness using automated segmentation and good responsiveness compared to manual segmentation (19). The responsiveness appears similar to our method, but as demonstrated by our results, patient selection (i.e., knees selected for loss or selected at random) has a major impact on responsiveness and limits the comparison of methods across samples drawn from different populations.

This study has some limitations. First, in longitudinal studies, bone surface area in the knees has been shown to increase with age (32,33). However, this limitation would likely affect the variable but have little effect on \( b \) and \( c \), and we present data on cartilage volume normalized to subchondral bone area as previously recommended, to provide satisfactory construct validity (34). Second, we have not included the patella, but this absence will be addressed in future work. Also, LACS can now be applied to the 4 tibiofemoral cartilage plates on 3D DESS MRI sequences; however, the previous version has also been used to quantify medial femur cartilage on 2D turbo spin-echo scans (35), and the current version can in principle be extended to other sequences such as the Multicenter Osteoarthritis Study (36). Third, we have not assessed the clinical validity. Finally, while highly efficient compared to manual segmentation, LACS nevertheless requires some reader time. Cartilage segmentation from MRI is moving toward the development of more fully automated methods using advanced multilevel, multidata, and multiapproach techniques to provide assistance in clinical studies (37). Deep learning methods can potentially offer a fully automated approach to LACS (38), and the current software is adequately efficient to segment several thousand MRI acquisitions that would offer a large amount of training data necessary for developing robust deep learning algorithms.

In conclusion, the updated LACS software allows for fast, reproducible, responsive, and valid quantification of cartilage loss on MRI in multiple areas of the knee joint. The coordinate system that underlies this method is computer-driven and based on anatomical landmarks, which allows for consistent longitudinal measurements of cartilage. We also present heatmaps, a parameterization of cartilage plate topography that could be used as a novel method to track cartilage loss over time. We anticipate that the updated LACS method will find applications in future clinical OA trials to monitor treatment response and potentially guide management decisions in patient care.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Mathiesen 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.

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