QIBA Profile: MR-based cartilage compositional biomarkers ($T_{1\rho}$, T_2) for the knee

Profile submitted by BC to MR CC for Stage 2: Consensus

Table of Contents

Change Log:

This table is a best-effort of the authors to summarize significant changes to the Profile.

55

Date	Sections Affected	Summary of Change
2017.09.18	All	First draft
2018.09.18		Second draft
2019.04.22		
2019.06.13		
2019.06.25		Draft before summer break
2019.10.05		Draft for committee review
2019.10.05		Draft for committee review
2020.04.25		update Michael Boss
2020.05.11		update Thomas Link - draft for committee review
2020.05.18		update Thomas Link - draft for committee review – sent out to BC
2020.01.23		update Thomas Link - address comments from public review
2021.07.11		update Xiaojuan Li and Thomas Link - implemented comments from public review

Open Issues:

The following issues are provided here to capture associated discussion, to focus the attention of reviewers on topics needing feedback, and to track them so they are ultimately resolved. In particular, comments on these issues are highly encouraged during the Public Comment stage.

Q. Calibration Phantom / Cross calibration A. Development of a calibration phantom for knee cartilage $T_{1\rho}$ and T_2 mapping, with reference T_1, $T_{1\rho}$ and T_2 values provided by NIST, is on-going as funded by NIH.
Q. Automated analysis algorithm A. work in progress – AI algorithm has been developed – needs to be applied
Q. Profile – 07-11-21 1. updated profile and implemented comments
Q. Profile 1. Update dashboards - https://docs.google.com/spreadsheets/d/1A7_uieyw0uu2DKbP6Vkzd37JuBEb2zmm-yqfXJtV-p4/edit#gid=134571965 2. Wikipage needs to be updated – needs to have a link to the profile
Q. Citations: Should be continuously numbered throughout Profile to avoid degenerate references **A. was changed – 5/12/20.**

1. Executive Summary

The goal of a QIBA Profile is to help achieve a useful level of performance for a given biomarker.

The **Claim** (Section 2) describes the biomarker performance.

The **Activities** (Section 3) contribute to generating the biomarker. Requirements are placed on the **Actors** that participate in those activities as necessary to achieve the Claim.

Assessment Procedures (Section 4) for evaluating specific requirements are defined as needed.

This QIBA Profile (**MR-based cartilage compositional biomarkers ($T_{1\rho}$, T_2)**) addresses the application of **$T_{1\rho}$ and T_2** for the **quantification of cartilage composition, which can be used as an imaging biomarker to diagnose, predict and monitor early osteoarthritis**. It places requirements on Acquisition Devices, Technologists, MRI Physicists, Radiologists, Reconstruction Software and Image Analysis Tools involved in Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image Quality Assurance (QA) and Image Analysis.

The requirements are focused on achieving sufficient reproducibility and accuracy for measuring cartilage composition.

The clinical performance target is to achieve a reproducibility of 4-5% for measurements of global cartilage composition with T_2 and $T_{1\rho}$ relaxation time measurements and a 95% confidence level for a true/critical change in cartilage composition (least significant change) with a precision of 11-14% and 9-12% if only an increase is expected (claim is one-sided). The target applies to 3T MR scanners of one manufacturer with identical scan parameters across different sites. It does not apply to scanners from different manufacturers.

This document is intended to help clinicians basing decisions on this biomarker, imaging staff generating this biomarker, vendor staff developing related products, purchasers of such products and investigators designing trials with imaging endpoints.

Note that this document only states requirements to achieve the claim, not "requirements on standard of care." Conformance to this Profile is secondary to properly caring for the patient.

Summary for Clinical Trial Use

The **MR-based cartilage compositional biomarkers profile** defines the behavioral performance levels and quality control specifications for $T_{1\rho}$, T_2 scans used in single- and multi-center clinical trials of osteoarthritis and other trials assessing cartilage composition longitudinally with a focus on therapies to treat degenerative joint disease. While the emphasis is on clinical trials, this process is also intended to be applied for clinical practice. The specific claims for accuracy are detailed below in the Claims.

The specifications that must be met to achieve conformance with this Profile correspond to acceptable levels specified in the $T_{1\rho}$, T_2 Protocols. The aim of the QIBA Profile specifications is to minimize intra- and inter-subject, intra- and inter-platform, and inter-institutional variability of quantitative scan data due to factors other than the intervention under investigation. $T_{1\rho}$ and T_2 studies performed according to the technical specifications of this QIBA Profile in clinical trials can provide quantitative data for single time-point assessments (e.g. disease burden, investigation of predictive and/or prognostic biomarker(s)) and/or for multi-time-point comparative assessments (e.g., response assessment, investigation of predictive and/or prognostic biomarkers of treatment efficacy).

A motivation for the development of this Profile is that while a typical MR $T_{1\rho}$ and T_2 measurement may be stable over days or weeks, this stability cannot be expected over the time that it takes to complete a clinical trial. In addition, there are well known differences between scanners and the operation of the same type of scanner at different imaging sites.

The intended audiences of this document include:

• Biopharmaceutical companies, rheumatologists and orthopedic surgeons, and clinical trial scientists designing trials with imaging endpoints.

• Clinical research professionals.

• Radiologists, technologists, physicists and administrators at healthcare institutions considering specifications for procuring new MRI equipment for cartilage measurements.

• Radiologists, technologists, and physicists designing $T_{1\rho}$ and T_2 acquisition protocols.

• Radiologists, and other physicians making quantitative measurements from $T_{1\rho}$ and T_2 sequence protocols.

• Regulators, rheumatologists, orthopedic surgeons, and others making decisions based on quantitative image measurements.

• Technical staff of software and device manufacturers who create products for this purpose.

Note that specifications stated as 'requirements' in this document are only requirements to achieve the claim, not 'requirements on standard of care.' Specifically, meeting the goals of this Profile is secondary to properly caring for the patient.

2. Clinical Context and Claims

Clinical Context

Osteoarthritis is a major health concern for our aging population and according to the National Center for Health Statistics the most frequent cause of disability in individuals older than 55 years (1). Symptomatic knee OA occurs in 10% of men and 13% of women aged 60 years or older and the number of people affected with symptomatic OA will increase due to the aging of the population and the obesity epidemic (2). In December 2016 the Pre-Competitive Consortium for Osteoarthritis, an initiative of the Osteoarthritis Research Society International, submitted a White Paper entitled Osteoarthritis as a Serious Disease to the U.S. Food and Drug Administration (https://oarsi.org/education/oarsi-resources/oarsi-white-paper-oa-serious-disease). Given the devastating impact on mobility and professional activity biomarkers for better risk assessment, diagnosis at early stages and monitoring of osteoarthritis will have a significant impact on public health. Noninvasive imaging biomarkers that would provide this information will transform health care delivery and management. There is a critical gap in the biomarker qualification process, which needs to be addressed in order to move these quantitative imaging biomarkers forward. Creating a profile for quantitative imaging of cartilage T_2 and $T_{1\rho}$ will allow to enhance development, potentially improve approval and facilitate application of this important imaging biomarker in the future.

Cartilage compositional imaging biomarkers allow earlier diagnosis, better prediction and more sensitive monitoring of early osteoarthritis of the knee. In particular, compositional cartilage biomarkers represent quantitative measures that could reduce the size and duration as well as increase the objectivity of clinical, multi-center trials. The key advantage of these measures is earlier detection before cartilage loss has happened and providing a truly quantitative, reproducible measurement.

While $T_{1\rho}$ and T_2 relaxation time measurements are the most frequently used cartilage compositional imaging biomarkers with the best available reproducibility data other biomarkers have been developed which include T2*, delayed Gadolinium MRI of Cartilage (dGEMRIC), Sodium imaging and chemical exchange saturation transfer imaging of glycosaminoglycans (gagCEST).

Quantifying the cartilage composition and measuring longitudinal changes within subjects; i.e. evaluating increase or decrease in T_2 and $T_{1\rho}$ relaxation times with image processing of MR scans acquired at different time points.

Conformance to this Profile by all relevant staff and equipment supports the following claim(s):

Claim 1A: Cartilage matrix T_2 relaxation time values are measurable with MRI at 3T with a within-subject coefficient of variation of 4-5% (test-re-test from the same vendor).

Claim 1B: Cartilage matrix $T_{1\rho}$ relaxation time values are measurable with MRI at 3T with a within-subject coefficient of variation of 4-5% (test-re-test from the same vendor).

Claim 2A: A measured increase/decrease in T_2 of 11-14% or more indicates that a true/critical change has occurred with 95% confidence. If only an increase in T_2 is expected (progressive cartilage matrix degeneration) the claim is one-sided and an increase of 9-12% represents a true/critical change. This claim applies to 3T scanners from the same vendor.

Claim 2B: A measured increase/decrease in $T_{1\rho}$ of 11-14% or more indicates that a true/critical change has occurred with 95% confidence. If only an increase in $T_{1\rho}$ is expected (progressive cartilage matrix degeneration) the claim is one-sided and an increase of 9-12% represents a true/critical change. This claim applies to 3T scanners from the same vendor.

Important considerations and limitations:

- The 11-14% (two-sided) or 9-12% (one-sided) in Claim 2 is the minimum detectable difference in $T_{1\rho}$ and T_2 values in a single patient over time. Clinical trials with larger sample sizes could potentially detect smaller differences based on the sample size, inter-subject and within-subject variations.
- Details of the claim were derived from a review of the literature summarized in Appendix B.
- Coefficients of variation will be calculated from mean values of $T_{1\rho}$ and T_2 in defined compartments as detailed in Section 3.7 (patella, trochlea, medial femur and tibia, lateral femur and tibia as well as global cartilage (3, 4)).
- The Claim requires presence of a significant amount of cartilage to be present and that there is no significant loss of cartilage volume and there are no major defects in the measured area. In order to focus on subjects with less severe cartilage loss, analyses should be restricted to patients with Kellgren-Lawrence (KL) Score of 0-2, or early stage disease. One important caveat that needs to be considered concerning patients with KL2 is presence of regions with full thickness cartilage loss in these knees as discussed below in the discussion.
- Claims do not apply for patients or subjects with KL scores ≥ 3.
- Claims were separated for $T_{1\rho}$ and T_2 measures, in particular to indicate that cartilage T_2 mapping sequences are available as a commercial product while $T_{1\rho}$ sequences are not. Once $T_{1\rho}$ sequences are available as a commercial product our profile will be modified to include new technical information and specifications.
- The current claims are for investigation of knee cartilage only. There are only a small number of studies using $T_{1\rho}$ and T_2 at the hip, with less standardization of measurements. The hip may be added at a later stage.
- While increase in $T_{1\rho}$ and T_2 measures is expected in early osteoarthritis indicating progressive cartilage degenerative change, decrease in $T_{1\rho}$ and T_2 measures may also be shown related to treatment/interventions and activities (5-7). The main focus of the claims is therefore on bi-directional change. We also acknowledge that concurrent increase and decrease in $T_{1\rho}$ and T_2 measures may be found in different regions of the same knee, which may be related to local differences in collagen synthesis/metabolism (8).

- The Claims are applicable for single and multi-center studies using the same 3T MRI scanners from the same manufacturer. While it is anticipated that for multi-center studies with MR imaging performed using the same scanner and protocol for each patient at each time point this Claim will be met, we do not anticipate that at this time the Claim will be met for scanners from different manufacturers.
- For both single and multi-center studies the Claim requires the use of calibration phantoms, which allows to check consistency of measurements (see 3.3. Periodic QA). A standard calibration phantom will be developed by NIST and is currently work in progress. It is anticipated that this phantom will be available in 2021.
- This Claim is based on manual, semi-automatic or automatic cartilage segmentation using dedicated analysis software. Cartilage segmentation software is currently not yet a commercial product. Semiautomatic and automatic segmentation algorithms have been developed using machine learning techniques by several research groups. Reproducibility data for semi-automatic techniques have been published (9). Semiautomatic and automatic segmentation algorithms technologies have also been validated (10).
- While the Claim has been informed by an extensive review of the literature, it is currently a consensus Claim that has not yet been substantiated by studies that strictly conform to the specifications given here. In addition, we note that this Claim should be re-assessed for technology changes. A standard utilized by a sufficient number of studies does not exist to date. The expectation is that from future studies and/or field testing, data will be collected and changes made to this Claim or the Profile specifications accordingly. An Arthritis Foundation funded study has been performed providing pilot data for inter-vendor inter-site reproducibility; the manuscript has been published by the Journal "Osteoarthritis & Cartilage" (3). A NIH funded study will allow rigorous reproducibility testing using scanners from the same and different manufacturers; it will also include development of a dedicated calibration phantom (available in 2021).

Discussion

These claims are based on estimates of the cartilage measurement coefficient of variation (wCV) for intact cartilage without significant cartilage loss. For estimating the critical % change, the % Repeatability Coefficient (%RC) is used: $2.77 \times wCV \times 100$.

The 11-14% boundaries can be thought of as "error bars" or "noise" around the measurement of compositional change. If you measure change within this range, you cannot be certain that there has really been a change. However, if cartilage composition changes beyond these limits, you can be 95% confident that there has been a true change in the cartilage composition, and the perceived change is not just measurement variability. Note that this does not address the biological significance of the change, just the likelihood that the measured change is real. Note also, that if a one-sided claim (increase only) is proposed 9-12% change will be required while for a two-sided claim 11-14% is necessary.

Clinical Interpretation: According to natural evolution studies we expect that an increase in $T_{1\rho}$ and T_2 measurements represents progressive degeneration of the cartilage matrix, which is driven by risk factors for OA such as obesity, previous injury (ACL tears) and high levels of physical activity (the larger the degeneration the larger the increase in $T_{1\rho}$ and T_2 measurements). The smaller the amount of longitudinal increase in $T_{1\rho}$ and T_2 measurements the less degeneration of the cartilage matrix is observed. Biochemical changes measured in the cartilage matrix are related to increase in water content, disruption of collagen architecture and loss of proteoglycans. It has also been shown that injury of the cartilage matrix related to marathon running is reversible, with decrease of T_2 measurements over 3 months (5).

In addition to $T_{1\rho}$ and T_2 measurements other biomarkers are available, which include dGEMRIC, Sodium imaging and gagCEST. These imaging biomarkers may be more specific to quantifying glycosaminoglycans but they have inherent limitations, which make them less suitable for clinical routine imaging. dGEMRIC requires intravenous application of Gd-DTPA (11), sodium imaging is performed with a dedicated coil and suffers from inherent low signal-to-noise-ratio (12, 13) and gagCEST needs high field strength imaging (7T) (14, 15). There is also limited reproducibility data available for these technologies.

While KL Score 0-2 knees are recommended to be included it needs to be considered that patients with KL2 knees not infrequently have regions with full thickness cartilage loss. According to work by Roemer et al. approximately 25% of knees with KL2 have wide-spread full thickness cartilage loss in the medial femoro-tibial joint compartment (mFTJ) and 11% in the lateral femora-tibial joint compartment (lFTJ) (16). Regarding absence of cartilage damage 20% of KL2 knees do not exhibit any cartilage damage in the mFTJ, while these numbers are 40% for the lFTJ and 15% for the patella-femoral joint compartment (PFJ). One third of KL2 knees exhibit only minimal cartilage damage in the MFTJ. Given the heterogeneity of cartilage damage in KL2 knees, radiography as an instrument to define which patients should undergo compositional cartilage imaging has limitations which need to be acknowledged.

3. Profile Activities

The Profile is documented in terms of "Actors" performing "Activities". Equipment, software, staff or sites may claim conformance to this Profile as one or more of the "Actors" in the following table.

Conformant Actors shall support the listed Activities by conforming to all requirements in the referenced Section.

Table 1: Actors and Required Activities

Actor	Activity	Section
Site	Staff qualification	3.1.
	Installation	3.2.
Acquisition Device	Installation	3.2.
	Periodic QA	3.3.
	Subject Handling	3.5.
	Image Data Acquisition	3.6.
Technologist	Staff qualification	3.1.
	Periodic QA	3.3.
	Subject Handling	3.5.
	Image Data Acquisition	3.6.
	Image Analysis	3.7.
Physicist	Development of MRI protocols	3.6.
	Development of analysis tools	3.7.
	Image Analysis	3.7.
	Periodic QA	3.3.
Radiologist	Subject Selection	3.4.

	Subject Handling	3.5.
	Image Analysis	3.7.
	Data interpretation	3.8.
Image Analysis Tool	Image Analysis	3.7.

The requirements in this Profile do not codify a Standard of Care; they only provide guidance intended to achieve the stated Claim. Failing to conform to a "shall" in this Profile is a protocol deviation. Although deviations invalidate the Profile Claim, such deviations may be reasonable and unavoidable and the radiologist or supervising physician is expected to do so when required by the best interest of the patient or research subject.

3.1. Staff Qualification

This activity involves evaluating the human Actors (Radiologist, Scanner Operator and Image Analyst) prior to their participation in the Profile.

While there are currently no specific certification guidelines for human actors, technologists and image analysts should be trained in technical aspects of cartilage $T_{1\rho}$ and T_2 measurements, including understanding key acquisition principles (patient positioning and image acquisition), quality criteria, and image analysis. The analyst should undergo documented training by a radiologist having qualifications conforming to the requirements of this profile in terms of anatomical location and image contrast(s) used to select measurement target. The level of training should be appropriate for the setting and the purpose of the measurements.

3.1.2 Specification

Parameter	Actor	Requirement
Qualification	Technologist/ Image Analyst	Shall undergo documented training by qualified physicist/radiologist in understanding key acquisition principles of the cartilage $T_{1\rho}$ and T_2 images as well patient positioning. Training by a qualified radiologist shall also include image analysis with regards to anatomical location and selection of measurement target.

3.2. Installation

Installation and initial validation will be performed according to manufacturer-defined procedures and specifications.

Pulse sequences, coils, phantom and segmentation software

Pulse sequences will be installed and are based on the recommendations of the previous cross-calibration study (3) (details are listed in section 3.6.). As coils have a significant impact on signal and measurements knee quadrature transmit/(minimum) eight-channel phased-array receive coils shall be used. In order to meet the claims identical coils need to be used for repeated, longitudinal measurements.

Conventional flexible coils can be used but need to meet conformance/reproducibility listed in the claims. In a previous study improved SNR and reduced fitting error were found using a receive only 16ch flex coil compared to a T/R 8Ch knee coil (4). It was also noted that $T_{1\rho}$ and T_2 values were significantly higher using the 16ch flex coil than those using the T/R 8Ch knee coil (P = 0.009, 95% CI = (0.4, 1.5) for T1ρ; P = 0.02, 95% CI = (0.4, 3.0) for T2).

Quality assurance: For repeated measurements, and if scanners at different sites are used a calibration phantom will be used to cross-calibrate the measurements across scanners and sites. The phantom will be used to assess reproducibility of $T_{1\rho}$ and T_2 measurements and can verify that the technical performance of the scanner meets minimum specifications in order to achieve the Claims (see 3.3. Periodic QA section). Performance of the scanner, the coil and pulse sequences shall be tested and reliably meet the profile claims (see 3.3). Note that different 3T scanners from the same manufacturer may have variability in measurements.

A phantom which was used for a previous Arthritis Foundation funded study is currently available at several sites (see reference 3 and 4 below). This is an agarose gel phantom that was informally referred to as ‘GE-NBA study’ phantom and was manufactured by The Phantom Laboratory (P.O. Box 511, Salem, NY, 12865-0511 USA).
An additional and standard calibration phantom will be developed by NIST and is currently work in progress. It is anticipated to be available in 2021.

Semi-automatic or automatic segmentation software needs to be installed that allows reproducible segmentation of the cartilage (see section 3.7).

3.2.1 Discussion

Measurements need to be calibrated with those performed at other sites using the same vendor and field strength. Not only should acquisition parameters be identical but analysis software needs to be standardized.

The long term goal is to develop a **calibration factor** that allows comparison of measurements between scanners from different manufacturers and sites. This requires a larger scale study and a multi-vendor multi-site study has been funded by the NIH/NIAMS (PI:

Xiaojuan Li, ongoing since 05/2020). Within the framework of this grant Dr. Li will work with Dr. Katy Keenan from NIST and Dr. Elizabeth Mirowski from Verellium Inc. to develop a calibration phantom (with a built-in thermometer and allowing not only quantitative compositional but also geometric measurements).

3.2.2 Specification

Parameter	Actor	Requirement
Qualification activities	Site	Shall perform qualification activities for MRI scanner, Scanner Operator, and Image Analyst to meet equipment (hardware and software), acquisition and image analysis required to achieve the claims
Acquisition requirements	Acquisition Device	Standardized sequences shall be installed as outlined in 3.6.
Acquisition requirements	Acquisition Device	Transmit/receive knee coils or flex coils (minimum eight-channel phased-array) meeting conformance with claims
Acquisition device performance	Acquisition Device	Calibration phantoms will be used to validate measurements and test reproducibility (also to compare sites and for quality assurance)
Acquisition	Technologist/Radiologist MR-Scientist/Physicist	Calibration phantoms will be used to validate measurements and test reproducibility
Cartilage segmentation	Image Analysis Tool	Manual, semi-automatic or automatic software that allows segmentation of cartilage with high reproducibility. To date no commercial product available, but semi-automatic and automatic tools were developed by multiple research groups

3.3. Periodic QA

Required QA:

Periodic QA procedures shall be performed once monthly using *the calibration phantom developed for cartilage quantitative assessment* (currently the phantom developed for AF foundation study (4)) and the small ACR phantom (for knee coil). Specific phantom holders need to be used to acquire the images (4, 17, 18). A specific NIST calibration phantom is currently under development and will be available in 2021. The phantom will be able to fit into knee coils used by the three major vendors (GE, Philips, Siemens) and contains 28 vials with T_1 ranging from 300ms – 1200ms, and $T_{1\rho}$ and T_2 ranging from 15ms – 105 ms. The phantom also contains one slice profile wedge, two resolution inserts, and MR readable thermometer.

Monthly and annual QA analyses shall be performed using automated image analysis software (e.g. SimplyPhysics, Baltimore, MD for the ACR phantom).

Hardware, software and coil changes/upgrades as well as change in calibration phantoms need dedicated QA sessions before and after the changes with calibration phantoms. Signal-to-noise ratio (SNR) of different coils may vary substantially between different coils.

Precision for each metric will be determined by first calculating the mean and variance of all measurements at the site individually. These calculations will be performed before and after any changes (see above) and will be pooled for overall reproducibility. The coefficient-of-variation (CV%) will be determined by the square root of the variance/mean^2. All outliers are included in the calculation to provide a realistic representation of the MR system variation. Systematic differences in metric values will be evaluated using a two-sided paired Student's t-test and Bland-Altman plot analysis for each study period.

3.3.1 Discussion

Performance specifications need to be equally restrictive as variations allowed by the manufacturer or the ACR as described by Schneider et al for the OAI (17, 18). Monthly QA with the phantoms should be used to identify and initiate service calls to correct drift or any other performance deficits in the MR system. Measurements should include signal-to-noise ratio (SNR), signal uniformity, geometry, and ghosting as suggested in (17, 18).

Previous work by Schneider et al on the OAI project demonstrated that quantitative phantom measurements were stable and only minor changes were found over 8 years using 4 identical Siemens 3T MRI systems (17, 18). Dardzinski et al showed that quadrature transmit/eight-channel phased-array receive coils provided higher SNR compared to quadrature transmit/receive coils (19). This resulted in improved reproducibility but also significantly longer T2 values for deep (all plates) and global (MT, cMF) cartilage.

Li et al. published reproducibility data and variations between different coils, GE MR systems and sites (4). Single-Site Study: The phantom longitudinal RMS-CVs ranged from 1.8% to 2.7% for $T_{1\rho}$ and 1.8% to 2.8% for T_2. Significant differences were found in $T_{1\rho}$

and T_2 values using different MR systems and coils. Multi-Site Study: The phantom longitudinal RMS-CVs ranged from 1.3% to 2.6% for $T_{1\rho}$ and 1.2% to 2.7% for T_2. Across three sites (n=16), the *in-vivo* scan-rescan RMS-CV was 3.1% and 4.0% for $T_{1\rho}$ and T_2, respectively. Phantom $T_{1\rho}$ and T_2 values were significantly different between three sites but highly correlated (R>0.99). No significant difference was found in $T_{1\rho}$ and T_2 values of traveling controls, with cross-site RMS-CV as 4.9% and 4.4% for $T_{1\rho}$ and T_2, respectively.

More recently, Kim et al reported the inter-vendor inter-site reproducibility of $T_{1\rho}$ and T_2 using MAPSS- $T_{1\rho}$-T_2 sequences at four sites with three vendors, Siemens, GE and Philips (3). The mean inter-site inter-vendor CVs in phantoms were 6.45% and 5.23% for $T_{1\rho}$ and T_2, respectively. The mean inter-site inter-vendor CVs in traveling volunteers were 8.14% and 10.06% for $T_{1\rho}$ and T_2, respectively.

Temperature has a significant impact on relaxation times (20-22). Significant changes in $T_{1\rho}$ and T_2 values with temperatures were reported using agarose gel phantoms (concentrations 2%-4%, weight/volume). $T_{1\rho}$ values decreased 1.17 to 2.02 ms every °C, and T2 decreased 1.07ms - 1.94ms every °C (23). Seasonal fluctuation of phantom T_2 values were reported (17,18). Therefore, calibration phantom needs to be stored in scanner room the night before the scan as temperature in scanner room is best controlled. It has been reported that the intra-articular knee temperature may vary with different health conditions of the knee joint in human subjects (24). However, no studies have reported the effect of temperature on in vivo cartilage $T_{1\rho}$ and T_2 measures in human subjects. It should be noted that temperature may also impact detection electronics or overall power levels into the various system components, and introduce variation of relaxation time measures for both phantoms and human subjects (17,18).

A calibration factor will be developed using the NIST phantom or patient volunteer data.

3.3.2 Specification

Parameter	Actor	Requirement
Calibration	Technologist, MRI Physicist	Shall perform calibration monthly using $T_{1\rho}$/T_2 and ACR phantom. Shall record the date/time of the calibration for auditing.
	Acquisition Device	Calibration phantom shall be suitable for performing the Calibration Factor assessment. Shall record the most recent Calibration Factor for use in subsequent activities.
Qualification	Physicist	QA shall be overseen by a Qualified Medical Physicist (QMP) as defined by AAPM.

3.4. Subject Selection

This activity describes criteria and procedures related to the selection of appropriate imaging subjects that are necessary to reliably meet the Profile Claim.

3.4.1 Discussion

Subject selection shall be based on the knowledge that patients with significant amounts of cartilage loss are not suited to undergo $T_{1\rho}$ or T_2 measurements (25). This is why only patients with relatively early disease or at least joint compartments with maintained cartilage shall be examined. We therefore recommend that only patients with radiographic Kellgren-Lawrence (KL) grade 0-2 shall be examined. Limitations are expected in patients with KL2 as these have frequently cartilage loss (as described in detail previously in the claims section).

Patients with metallic implants such as plate and screw internal fixation and metal artifacts on the MR images shall not undergo compositional imaging as this may alter T1rho/T2 values. Patients with ACL reconstruction can be included but compartments affected my metal artifacts should be excluded.

Indications for $T_{1\rho}$ and T_2 measurements are:

Overall goal is risk assessment and monitoring of interventions/management

1. Patients with **early osteoarthritis** (without significant joint space narrowing, ideally patients with no radiographic or only mild osteoarthritis consistent with Kellgren-Lawrence grade 0-2). Indications may be risk factors for osteoarthritis such as obesity, partial meniscectomy, family history, or high level of physical activity such as may be found in runners or other athletes. It may also be used in patients with chronic knee pain and no or limited evidence of degenerative changes on standard radiographs.
2. In **acute and chronic injury** $T_{1\rho}$ and T_2 may provide information on the degree of cartilage matrix injury.
3. In patients who are undergoing **high tibial osteotomy or unicompartmental prostheses** $T_{1\rho}$ and T_2 measurements may provide information on the cartilage quality of the non-damaged joint compartment.
4. $T_{1\rho}$ and T_2 may also be used to **monitor interventions** such as weight loss (6, 7, 26) and physical activity (5, 27-29) or pharmacotherapy (limited evidence).
5. $T_{1\rho}$ and T_2 may be used to monitor **cartilage repair** maturation.
6. $T_{1\rho}$ and T_2 may be used to monitor cartilage changes after surgery (such as ACL reconstruction, meniscal repair).

3.4.2 Specification

Parameter	Actor	Requirement
Clinical findings	Clinician	Needs to know limitations and indications of $T_{1\rho}$ and T_2 measurements.
	Radiologist	Needs to know limitations and indications of $T_{1\rho}$ and T_2 measurements.

3.5. Subject Handling

This activity describes details of handling imaging subjects that are necessary to reliably meet the Profile Claim.

Subjects shall be examined after having rested in a seated position for 30 minutes, however, patient can walk to the scanner. Patients should not have exercised on the day of the exam (no high impact sports, no running or ball sports, regular walking is fine). They should not have performed any unusual, atypical physical activities (such as a marathon or an extended hike) 48 hours before the MRI examination. The entire process should not take longer than 1 – 2 hours; longer times may result in push-back both by the radiology site and the patient.

Before $T_{1\rho}$ and T_2 sequences, anatomical high resolution sequences shall be obtained which adds to the rest time.

In order to achieve reproducible imaging and minimal motion standard MRI positioning aids such as leg/knee holders or foam cushions and positioning straps shall be used. Ankles and legs shall be sandbagged and positioning straps shall be used during the MRI scan to avoid motion in patients/volunteers. Subject-specific landmarking during MR scan shall be centered on the knee, which shall be located as close as is feasible to magnet isocenter. Reproducible positioning inside the coil is critical. Positioning has been described in detail in the OAI protocol (https://nda.nih.gov/oai/study-details).

3.5.1 Discussion

Subject handling is based on the fact that biomechanical loading may impact $T_{1\rho}$ and T_2 measurements including running (5, 29), and daily activities (30).

Patient should be in a seated position prior to the scan for a minimum of 30 minutes to avoid changes in $T_{1\rho}$ and T_2 related to biomechanical loading. Alternatively patient may be in a supine position for 30 minutes, or patient may be lying in the MRI scanner while non-quantitative sequences are performed (may be more difficult to standardize, however).

The entire process should not take longer than 1 – 2 hours; longer times deemed to result in push-back both by the radiology site and the patient. It will be important to request information regarding subjects' typical physical activities prior to scheduling. Physical activities defined as "moderate" or "strenuous" may vary from patient to patient and may need to be defined. As a general rule subjects should not engage in strenuous exercise within 48 hours prior to the scan (activity control).

Staff should make every attempt to ensure patient is comfortable prior to beginning the scans- provide ear plugs and ear phones if available and provide status updates to patient as routinely would in between scans.

3.5.2 Specification

Parameter	Actor	Requirement
Exam preparation	Technologist	Need to make sure that patient rests 30 minutes before the scans and has not performed strenuous exercise with 48 hours of the exam.
	Radiologist	See above

3.6. Image Data Acquisition

Standardized $T_{1\rho}$ and T_2 sequences (MAPSS):

The $T_{1\rho}$ and T_2 imaging sequence will be based on the magnetization-prepared angle-modulated partitioned k-space spoiled gradient echo snapshots (MAPSS) acquisition that were previously developed and have been validated in a multi-site multi-vendor study sponsored by the Arthritis Foundation, **Fig. 1** (3, 4, 31). The $T_{1\rho}$ preparation pulses contain continuous hard 90_x (tip-down pulses) - spin lock pulses - $90°_{-x}$ (tip-up pulses). The sequence uses 4 echos for $T_{1\rho}$ and 4 echos for T_2 as shown in Table 3. Composite tip-up and tip down pulses are applied to improve robustness to B_0 inhomogeneity (32). The phase of the second half of the spin-lock pulse is shifted 180° from the first half to reduce artifacts caused by B_1 inhomogeneity (33). Multiple k-space lines (views per segmentation, VPS) are acquired immediately after each magnetization preparation. RF cycling is applied to eliminate the adverse impact of longitudinal relaxation on quantitative accuracy. This RF cycling scheme also yields a transient signal evolution that is independent of the prepared magnetization, and consequently the same variable flip angle train can be applied to provide a flat signal response to eliminate the

filtering effect in k-space caused by transient signal evolution after each spin-lock. The T_2 preparation contains an MLEV (**M**alcolm **Lev**itt's composite-pulse decoupling sequence) train of nonselective composite $90°_x 180°_y 90°_x$ refocusing pulses.

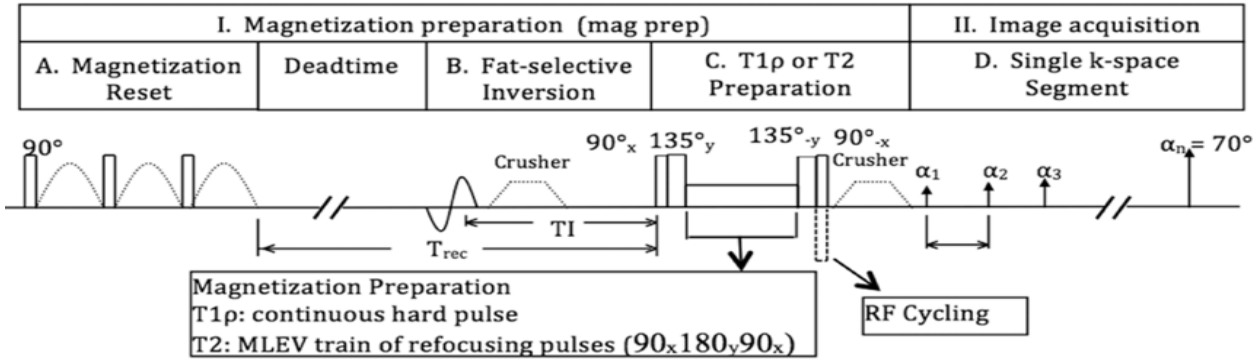


Fig. 1: The MAPSS-based $T_{1\rho}$ and T_2 imaging sequence is available as research prototype by the three major MR vendors including GE, Siemens and Philips.

High resolution sequences for segmentation and registration:

High resolution images are needed for performing reliable and reproducible cartilage segmentation, as well as registration between scans. 3D gradient-echo based sequences are normally recommended. The recommended sequences are DESS (product sequence on Siemens scanners, research patch on on Philips scanners), and MENSA (product sequence on GE scanners) as they provide good spatial resolution and contrast, but alternatively SPGR (GE), FLASH (Siemens) and FFE (Philips) can also be used (34) (**Table 2**). MAPSS sequences with recommended resolution in Table 3 should not be used for segmentation.

$T_{1\rho}$ and T_2 sequences (MAPSS):

Parameters for the MAPSS and high resolution gradient echo sequences are provided in **Table 3**, which should also provide sufficient image quality and signal to noise ratio. Minimal TR and TE are recommended to use for the readout to minimize scan time (min TR) and maximize SNR (min TE). The minimal TR and TE on each MR systems can be different due to different hardwares (e.g. different gradient performance), which has minimal effect on $T_{1\rho}$ and T_2 quantification. The reproducibility reported in Reference 3 and 4 were based on different TR/TE from different MR systems. Other parameters listed in Table 3 shall be consistent for single study or trial.

The calibration phantom described above will be scanned at center, left (60 mm) and right (60 mm) using the protocol in **Table 3** ($T_{1\rho}$ and T_2 sequences only). Geometrical phantom included in the phantom (NIST) will be used for high-resolution imaging.

3.6.1 Discussion

The local extremity SAR using the transmit/receive knee coil and recommended MAPSS $T_{1\rho}$ imaging protocol with spin-lock frequency at 500Hz (Table 3) is <20% of the safety limit. When the body transmit and receive-only flex coil is used, the MAPSS $T_{1\rho}$ imaging may not able to run at spin-lock frequency at 500Hz, either due to SAR exceeding safety limit or RF amplifier fault. In such case, it is recommended to reduce the spin-lock frequency to 400Hz. It needs to be noted that the $T_{1\rho}$ value will decrease with spin-lock frequency of 400Hz as compared to 500Hz due to $T_{1\rho}$ dispersion. It is recommended to use the same coil for all subjects in a single study or trial. The variations of $T_{1\rho}$ and T_2 values with different times of recovery, views per segment, with and without parallel imaging acceleration have been tested in Reference (3). Average CV=0.4% was reported, suggesting minimal variations with changes in these parameters.

Gradient-echo based sequences provide the most optimal delineation of cartilage edges and therefore are considered the gold standard reference sequences for cartilage segmentation and quantification. Spin-echo based sequences tend to have signal loss at the deep layer of cartilage, although 3D fast spin-echo sequences (such as CUBE/SPACE/VISTA on GE/Siemens/Philips) have also been used in the literature for cartilage segmentation (35). In summary based on results of previous work we would recommend gradient-echo based sequences as standards for segmentation.

Number of echoes: Three echoes is minimum and 4-8 echoes are recommended as using fewer echoes may introduce significant bias and poor reproducibility of estimating T1ρ and T2 values. Studies in the literature showed good reproducibility using 4 or 8 echoes. Four echoes are recommended as the default with the consideration of scan time. The optimized number of echoes and optimized echo spacing for T1ρ and T2 fitting is an active area of research.

Parallel Imaging for image acquisition is recommended to reduce acquisition time. Acceleration factor of 2 in phase direction has been used in studies in the literature. Higher acceleration factor may be used with improved coil structure. Promising results have been demonstrated using compressed sensing to accelerate cartilage $T_{1\rho}$ and T_2. Accuracy and precision need to be evaluated when advanced accelerating techniques are applied.

The MAPSS $T_{1\rho}$ and T_2 imaging is recommended as the preferred method based on the sequence robustness and reproducibility evaluation. Other sequences as discussed below may be used when MAPSS $T_{1\rho}$ and T_2 are not accessible, provided the Test-Retest Conformance as detailed in 4.2 can be met. The MAPSS $T_{1\rho}$ and T_2 imaging sequence is also available at 1.5 Tesla, but the recommended field strength is 3 Tesla.

Multi spin multi echo (MSME) sequences have been used to measure cartilage T_2 in previous studies, such as the OAI. While these sequences are available as products from all major MR vendors and have shown good reproducibility across different sites for one vendor (Siemens), Balamoody et al reported significant differences in T_2 measures between vendors, with inter-vendor mean T_2 differences ranging from 5.4 to 10.0 ms (~10% to 25%) (36). The sequence is also well known to be prone to variations introduced by stimulated echoes and magnetization transfer effects (37). The OAI protocol is recommended to be used as detailed in (38). In the OAI protocol, the first echo needs to be skipped during T2 fitting in order to minimize the potential bias (39).

We acknowledge that multiple other sequences are being developed by different research groups. These include quantitative double echo in steady state (qDESS) acquisition for T_2 measurement (40) and T1ρ-prepared magnetization-prepared pseudo-steady-state 3D fast spin-echo sequence (CubeQuant-T1ρ) (41). To date knowledge about reproducibility for these sequences across different scanners and platforms is limited. Research is evolving and updates will be provided in future profiles to include the newer sequences especially if the vendors come up with some products and intersite reproducibility data is available.

3.6.2 Specification

TABLE 2. SUGGESTED IMAGING PROTOCOL (FOR ALL VENDORS) HIGH RES GRAD ECHO SEQUENCE (3)

Parameter	Actor	Requirement	Dicom Tag
Field Strength	Acquisition Device/ Technologist	3.0T	
Acquisition Sequence		DESS (Siemens) MENSA (GE) are recommended alternatively SPGR/MFFE	
Coil type		Transmit/receive phased-array knee coil (8-channels or more)	
Acquisition time		6-8 min	
Matrix (freq x phase)		~384x300	
Number of slices		96-160	
Slice thickness (mm)		0.7-1.0	
Field of view (mm)		140-160	
Flip angle (deg)		10-25	
Echo time (TE) (ms)		Min (3-6)	
Repetition time (TR) (ms)		Min (8-15)	
Bandwidth (Hz/Px)		~186	

TABLE 3. SUGGESTED IMAGING PROTOCOL (FOR ALL VENDORS) 3D $T_{1\rho}$ AND T_2 MAPSS (3)

Parameter	Actor	Requirement	Dicom Tag
Field Strength	Acquisition Device/ Technologist	3.0T	
Acquisition Sequence		3D $T_{1\rho}$ and T_2 MAPSS	
Coil type		Transmit/receive phased-array knee coil (8-channels or more)	
Acquisition time		6-12 min (for 4-8 echo images)	
Matrix (freq x phase)		256~320 × 128~160	
Number of slices		24~32	
Slice thickness (mm)		3~4	
Field of view (mm)		140 ~ 160	
Flip angle (deg)		VFA	
Echo time (TE) (ms)		Min (2~4)	
Repetition time (TR) (ms)		Min (6~9)	
Bandwidth (Hz/Px)		~400	
Time of spin-lock (TSL)/Prepared TE (ms)		0/10/40/80 for $T_{1\rho}$ 0/10/30/60 for T_2	
Spin-lock frequency		500Hz (transmit/receive knee coil) or 400Hz (receive-only flex coil if needed)	

3.6.3. Access to MAPSS-$T_{1\rho}$-T_2 sequences and cartilage segmentation

The sequence is currently a research sequence and not generally available, however, sequences/patch may be obtained through a point person from the vendor or through special webpages.

Contact details to get MAPSS-$T_{1\rho}$-T_2 sequence/patch:

The MAPSS-$T_{1\rho}$-T_2 patch is not certified by the vendors and is not supposed to be considered as a medical device provided by the vendors.

Philips: The MAPSS-$T_{1\rho}$-T_2 sequence on Philips can be disseminated as a site-to-site collaboration between Philips sites who are interested in having the sequence and Albert Einstein College of Medicine. Please contact both Dr. Qi Peng (dr.chrispeng@gmail.com) at Albert Einstein College of Medicine and Dr. Yansong Zhao, PhD (yansong.zhao@philips.com) at Philips. The site needs to have a research agreement with Philips and clinical science keys that allow patch installation on the scanner.

Siemens: The MAPSS-$T_{1\rho}$-T_2 sequence on Siemens can be disseminated as a site-to-site collaboration (C2P) between the Siemens sites who are interested in having the sequence and the Cleveland Clinic. Please contact both Dr. Xiaojuan Li (lix6@ccf.org) at Cleveland Clinic and Dr. Kecheng Liu (kecheng.liu@siemens-healthineers.com) at Siemens. The sites need to have a research agreement with Siemens and IDEA license.

GE: With support from Dr. Sharmila Majumdar, UCSF, GE has the MAPSS-$T_{1\rho}$-T_2 sequence available through the GE Collaboration website (URL: https://collaborate.mr.gehealthcare.com/groups/mr-software-sharing). For GE sites who have (1) an EPIC license and (2) have signed the software sharing agreement, they can access the list of available third party research prototypes and contact details. In the case of GE sites who are interested in getting the MAPSS prototype, they would need to have both (1) and (2) above, they will enter the software sharing website and find the contact info for Misung Han, PhD at UCSF. Dr. Han will then cross-check their name with GE's software sharing list and grant them access to the MAPSS prototype on Dr. Han's managed github folder.

3.7. Image Data Analysis

Global and compartment specific analysis:

Ideally cartilage shall be segmented on high-resolution gradient echo images (DESS, MENSA etc outlined in **Table 2**) as previously proposed by Eckstein et al. (42). Six compartments shall be defined: patella (P), trochlea (TrF), lateral and medial femoral condyles (LF and MF), lateral and medial tibia (LT and MT). The LF/MF can be further divided into sub-compartments with regard to the menisci as shown in **Fig. 2**.

The segmentation shall be overlaid to $T_{1\rho}$ and T_2 maps. Mean and standard deviation of $T_{1\rho}$ and T_2 values shall be calculated for each defined compartment (43).

High-resolution anatomic images, as well as all $T_{1\rho}$- and T_2-weighted images shall be registered to the first echo of the $T_{1\rho}$-weighted images.

The $T_{1\rho}$ and T_2 maps shall be reconstructed pixel-by-pixel by fitting the $T_{1\rho}$- and T_2-weighted images based on equations $S(TSL) = S_0 \exp(-TSL/T_{1\rho})$ and $S(TE) = S_0 \exp(-TE/T_2)$, respectively.

Manual, semi-automatic or automatic segmentation software shall be used. However, requirements for reproducibility errors for the segmentation shall be in the order of 1.5% vs 2.2% for the whole knee cartilage segmentation as previously described by Stehling et al. (9).

Online reconstruction of T_2 maps is available on MR systems (CartiGram on GE scanner, MapIt on Siemens scanners, and T_2 mapping on Philips scanners) but there are no cartilage specific tools and to date there is no standardization. None of the vendor products allows to produce compartment specific quantitative $T_{1\rho}$ and T_2 data.

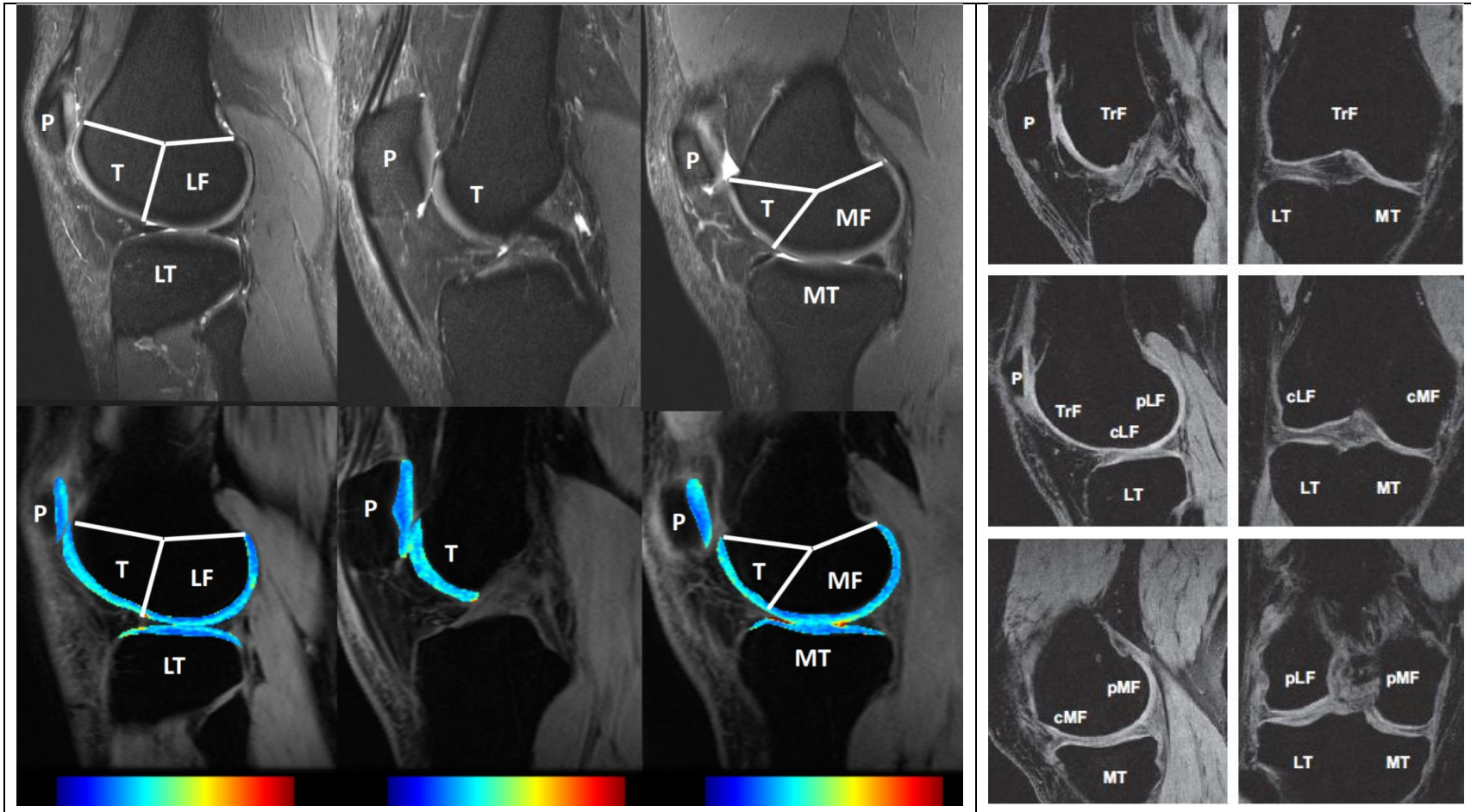


Fig. 2. Knee cartilage compartments with anatomical labels implemented in lateral, central and medial MR images obtained with an intermediate weighted fat-saturated fast spin echo sequence (left, top row) and a T1ρ MAPSS sequence (left, bottom row show T1ρ maps). Cartilage compartments can be subdivided (right image) using anatomical labels of knee joint cartilage plates according to reference (42). (P=patella, TrF/T=trochlea, LT=lateral tibia, MT=medial tibia, LF=lateral femur, MF=medial femur, cLF=central lateral femur, pLF=posterior lateral femur, cMF=central medial femur, pMF=posterior medial femur).

Lesion specific analysis:

Lesion specific analysis for areas of cartilage repair and evolving cartilage lesions shall be performed according to a previously published study (44). Regions of interest will be manually drawn around the lesion area in all slices. The surrounding cartilage shall be used as a control region. The segmentation of the "surrounding" cartilage shall include all the remaining clearly distinguishable cartilage of the articular plate of one of the following anatomical regions: medial (MFC) or lateral femoral condyle (LFC), medial (MT) or lateral tibia (LT), patella (P) or trochlea (T) (**Fig.3**). Analysis shall take magic angle effects into consideration.

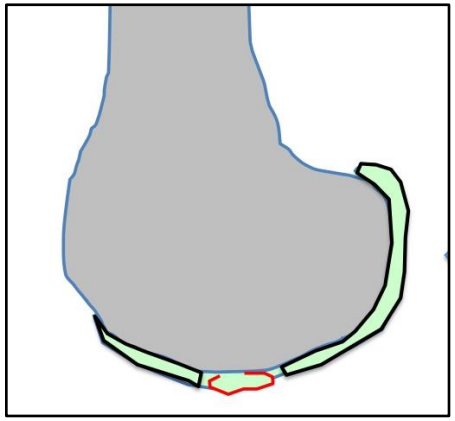


Fig. 3: Segmented lesion in red and surrounding control cartilage in black.

3.7.1 Discussion

In clinical trials, centralized data processing is needed to avoid variation introduced by different software for relaxation time fitting and cartilage segmentation.

We acknowledge that the regions of interest we propose are large, which may result in averaging out local changes. Smaller regions have been proposed in previous studies subdividing femoral, tibial and patellar cartilage layers (45, 46). Differentiating superficial and deep cartilage layers have also been proposed (47). While smaller regions may be more sensitive to change, subdivision may also decrease reproducibility, which would directly affect the claims of this profile. We therefore did not include smaller regions of interest but kept those shown in Figure 2. If smaller regions are used appropriate (and increased) spatial resolution may be required and and reproducibility needs to be in conformance with claims.

Performing registration between different $T_{1\rho}$- and T_2-weighted images will minimize bias introduced by potential subject motion during data acquisition. Rigid registration is normally sufficient between different echo images of $T_{1\rho}$ and T_2 imaging. For cases with motion that are not aligned satisfactorily with rigid registration, piece-wise (separated for each bone) rigid registration or non-rigid registration can be applied. Piece-wise rigid registration or non-rigid registration will be needed to register between the high-resolution anatomical images and $T_{1\rho}$ and T_2 images, or images collected during different exams.

Non-linear fitting is recommended which provides more reliable results compared to linear fitting (48, 49) (50). It shall be noted that estimates of $T_{1\rho}$ and T_2 can be biased due to low SNR and signal distortions with multi-element phased array coils. Fitting methods using noise correction, look-up table correction, and maximal likelihood estimate have been suggested to mitigate the bias (49, 50). At least three echoes images are needed for reliable fitting, and 4-8 echoes are recommended. This profile focused on mono-exponential fitting. Bi-exponential or multi-exponential decay fitting will require larger number of echoes and higher SNR of images.

To reduce artifacts caused by partial volume effects with synovial fluid or poor fitting, pixels with implausible values (e.g. $T_{1\rho} > 150$ ms, $T_2 > 130$ ms) or poor fits (e.g. r-squared < 0.8) shall be excluded from analysis.

There are a large number of publications on cartilage segmentation methods, including manual, semi-automatic and automatic-segmentation methods (51). The operator needs to be trained rigorously if manual or semi-automatic segmentation will be used. For automatic segmentation methods reproducibility and accuracy (using manual or semi-automatic segmentation) should be known.

More recently, deep-learning based methods have been developed for automatic segmentation of cartilage (52-54). Such automatic segmentation methods are promising for facilitating future clinical translation of advanced quantitative imaging techniques.

Magic angle effect, or the orientation dependency to collagen fibers, have been observed in T_2 and $T_{1\rho}$ imaging (55-57). The orientation dependency is less in $T_{1\rho}$ imaging due to the spin-lock compared to T_2 imaging (39), and such orientation dependency diminished at spin-lock frequency higher than 1KHz (37) or 2KHz (58). Consistent knee and feet positioning during data acquisition and matched-region analysis during data processing are strategies to minimize the effect of magic angle effect on data interpretation.

For patients with metal implants, the compartments that are affected by metal artifacts shall be excluded during data analysis.

Additional information from T_2 and $T_{1\rho}$ maps may be obtained by using texture analysis. Texture analysis algorithms provide information on homogeneity of cartilage as visualized on T_2 and $T_{1\rho}$ maps, a more heterogeneous texture is found with increasing degenerative changes of the cartilage matrix (59, 60). Current limitations with these techniques are lack of standardization.

3.7.2 Specification

Parameter	Actor	Requirement
Global analysis	Technologist/ image analyst	Perform semi-automatic or automatic segmentation and including registration
Lesion specific analysis	Radiologist/ image analyst	Perform manual, semi-automatic segmentation of lesion and surrounding tissue

3.8. Image Data Interpretation

Using standardized acquisition parameters (described in 3.6) and image analysis (described in 3.7) as well as calibration phantoms standardized $T_{1\rho}$ and T_2 values are generated. $T_{1\rho}$ and T_2 values will be reported for the global knee and 6 cartilage compartments (patella, trochlea, medial and lateral femur and tibia).

Based on the claim of our profile data interpretation will focus on longitudinal changes of cartilage composition.

Alternatively we can focus on the contralateral knee as a reference, but given that cartilage degeneration in the contralateral may be asymptomatic this approach has limitations.

The long term goal is to develop a **reference database of normal, healthy individuals**.

However, reference databases are not part of QIBA profiles, and we believe that this is beyond the scope of our profile. In the discussion we have included previous studies that describe a reference database for T_2 measurements and a risk score.

3.8.1 Discussion

A normal reference database would include healthy individuals that would be defined as men and women who have no signs or symptoms of OA. This would include no knee pain, no radiographic knee OA (KL0 and 1) and no cartilage defects on MRI. Given the high prevalence of cartilage lesions in asymptomatic and KL0/1 knees compartment specific reference values would be generated for cartilage $T_{1\rho}$ and T_2. An age range from 18-80 years would be useful. Given the complexity of generating normative values it would be important to use cross-calibration to be able to apply reference data for different scanners and sites. In addition to provide a more standardized approach to therapy **Z-scores** would be introduced. Analogous to BMD measurements (https://www.iscd.org/official-positions/2019-

iscd-official-positions-adult/) a Z-score >2 could be defined as significantly increased risk of progressive knee joint degeneration (using radiographic and MRI structural outcomes).
In addition **risk scores** could be developed that would include clinical and radiographic parameters (presence/absence of risk factors) and allow to better predict risk scores.

To date a large scale normative cartilage T_2 database is available from the Osteoarthritis Initiative data (**Table 4**) (39). This gender, age and BMI-specific reference database of cartilage T_2 values is based on 481 subjects aged 45-65 years with radiographic Kellgren-Lawrence Scores 0/1 in the study knee. Baseline T_2 measurements (resolution = 0.313 mm x 0.446 mm) were performed in the medial and lateral femurs, medial and lateral tibias, and patella compartments and a logarithmic transformation was applied to the data to obtain the 5th-95th percentile values for T_2. This database demonstrated significant differences in mean cartilage T_2 values between joint compartments. Although females had slightly higher T_2 values than males in a majority of compartments, the differences were only significant in the medial femur ($P < 0.0001$). A weak positive association was seen between age and T_2 in all compartments, most pronounced in the patella (3.27% increase in median T_2/10 years, $P = 0.009$) (**Figure 4**). Significant associations between BMI and T_2 were observed, most pronounced in the lateral tibia (5.33% increase in median T_2/5 kg/m(2) increase in BMI, $P < 0.0001$), and medial tibia (4.81% increase in median T_2 /5 kg/m(2) increase in BMI, $P < 0.0001$). Note that OAI data were acquired usind optimized conditions, with a single vendor, identical scanners, sequences and field strengths, which may not generalizable if different scanners and acquisition techniques are used.

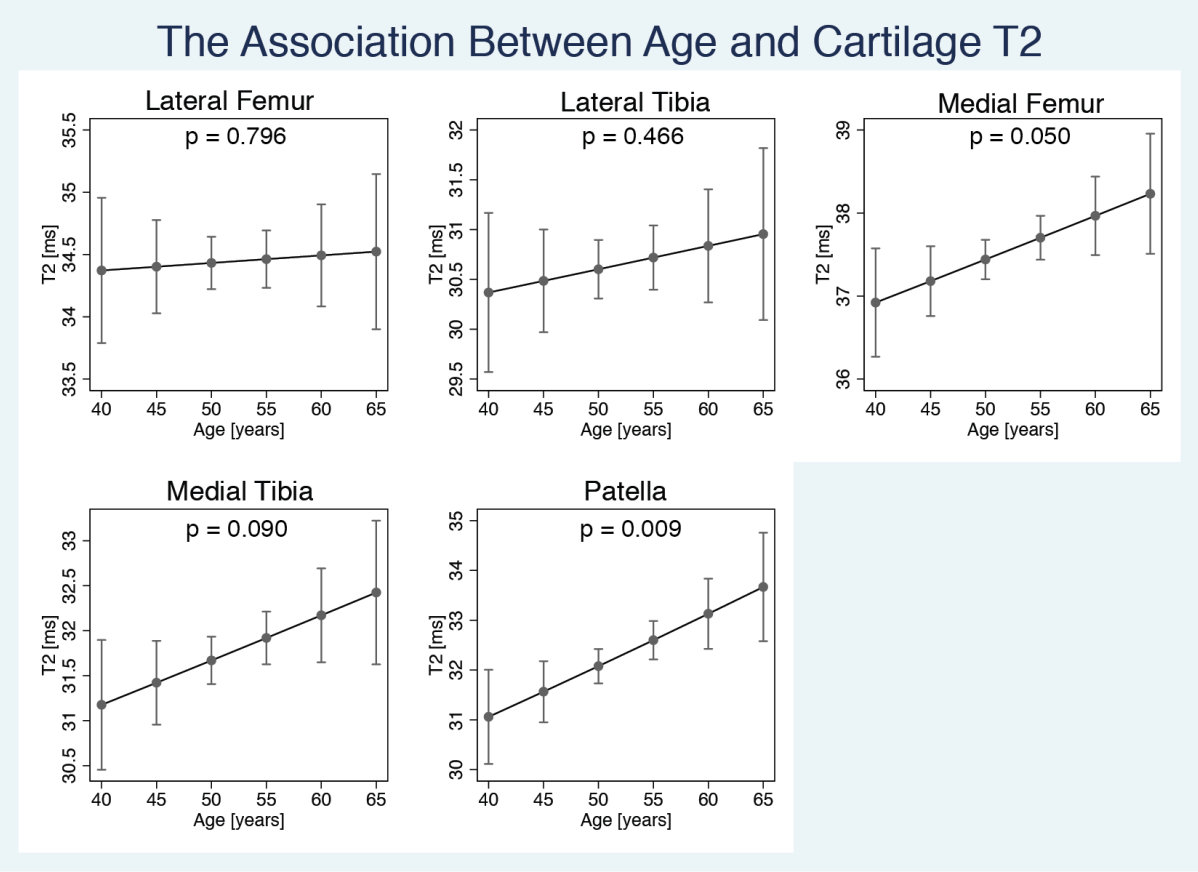
Table 4: Reference database of percentiles of T_2 values (in ms) in subjects with compartment-specific cartilage scores of WORMS 0/1 subdivided by gender*

645

	N	5%	10%	25%	50%	75%	90%	95%
Females								
Lateral Femur	236	30.936	31.718	33.069	34.639	36.284	37.830	38.785
Lateral Tibia	212	25.647	26.661	28.447	30.574	32.860	35.061	36.448
Medial Femur	225	34.092	34.925	36.362	38.030	39.775	41.412	42.423
Medial Tibia	250	26.838	27.781	29.432	31.383	33.464	35.453	36.698
Patella	163	27.748	28.711	30.396	32.387	34.508	36.533	37.801
Males								
Lateral Femur	207	30.979	31.661	32.835	34.192	35.604	36.925	37.738
Lateral Tibia	192	25.371	26.440	28.328	30.588	33.027	35.386	36.877
Medial Femur	198	33.476	34.219	35.497	36.974	38.514	39.952	40.838
Medial Tibia	218	27.287	28.287	30.042	32.122	34.346	36.477	37.814
Patella	172	27.637	28.582	30.233	32.182	34.256	36.235	37.473

* A logarithmic transformation was applied to the data to obtain a normal distribution, and percentile values of the log-transformed T2 data were calculated (using means and standard deviations) in each compartment. Finally, the data was reverse-transformed to quantify T2 values for various percentiles of the sample.

Figure 4: Association between age and cartilage T_2 in each joint compartment (with WORMS scores of 0/1). Figure shows adjusted means with 95% confidence intervals.



To address standardization issues related to hardware and software Z-scores shall be used; global and compartment specific Z-scores for $T_{1\rho}$ and T_2 values are obtained by calculating the standard deviation compared to healthy reference global or compartment specific cartilage using the equation:

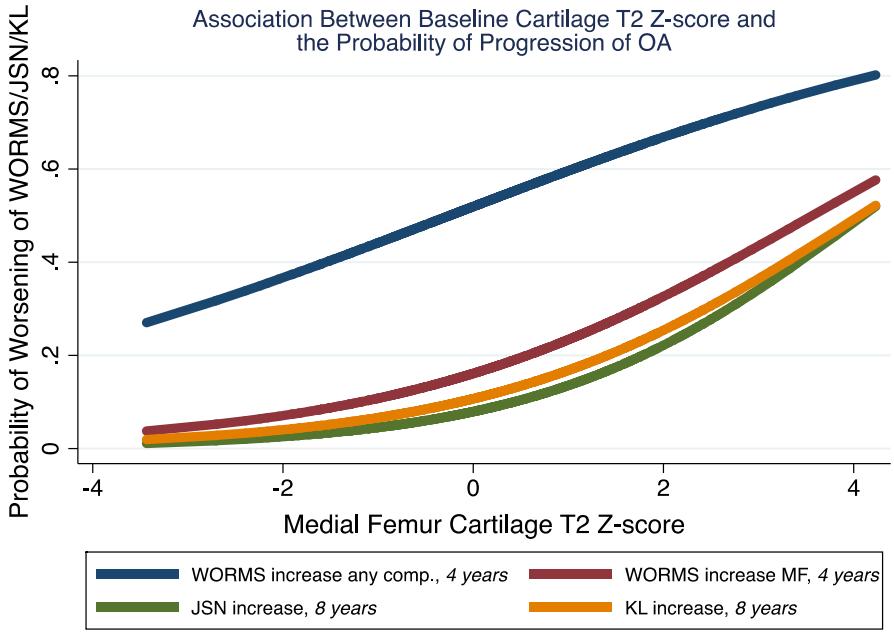
$$\text{Z-score} = \frac{Measured\ \ cartilage\ T2 - Reference\ cartilage\ T2\ mean}{Reference\ cartilage\ T2\ SD}$$

Using these standardized values, an individual's risk for progressive degenerative changes in the knee may be predicted, similar to the role of T-scores for bone mineral density in osteoporosis.

Joseph et al calculated cartilage T_2 Z-scores based on the probability of structural worsening of knee cartilage and whole joint degeneration over 4-8 years (61). They studied right knees with radiographic Kellgren-Lawrence (KL) grades of 0-2 in 587 participants from the Osteoarthritis Initiative (OAI). 3T MRI images were used to perform baseline cartilage T_2 quantification and assess 4-year changes in morphologic cartilage damage (WORMS scoring) in 5 cartilage regions (medial/lateral femur, medial/lateral tibia, patella). Changes in radiographic Joint Space Narrowing (JSN) and KL grade were assessed over 8 years. T_2 Z-scores were based on a reference database of knees without morphologic cartilage degeneration at baseline. Odds ratios for, and predicted probabilities of any worsening in WORMS cartilage, JSN and KL grade were obtained from logistic regression models. They found that a one unit increase in the baseline medial femur T_2 Z-score was associated with cartilage worsening in the same region (odds ratio: 1.59; $p<0.0001$ and in any region (OR: 1.37; $p<0.0001$), and with worsening JSN (OR: 1.82; $p < 0.0001$) and KL grades (OR: 1.69; $p<0.0001$). Predicted probabilities of worsening in knees with a medial femur T_2 Z-score

from 2-4 were 38% for WORMS cartilage in the medial femur, 70% in any region, 28% for increasing JSN and 31% for increasing KL grade. Based on their study cartilage T_2 values that are 2 to 4 SDs above the mean reference values (especially in the medial femur) are significantly more likely to have structural worsening of knee OA over 4 to 8 years (**Figure 5**).

Figure 5: The predicted probability of worsening of KL score over 8 years (orange), JSN change over 8 years (green), WORMS score in the medial femur over 4 years (MF, red), and WORMS change in any region over years (blue). Modeled values are based on logistic regression models with baseline cartilage T_2 Z-score in the medial femur as a predictor. For all outcomes, the probability of incidence/progression increases as a function of cartilage T_2 Z-score in the medial femur. The figure shows the associated probabilities of incidence/progression based on categorical values of cartilage T_2 Z-scores in the medial femur.



By defining a Z-score of greater 2 as indicating an increased risk of joint degeneration we would eliminate absolute T_2 and $T_{1\rho}$ values in data interpretation. We would still need normal reference values for an individual.

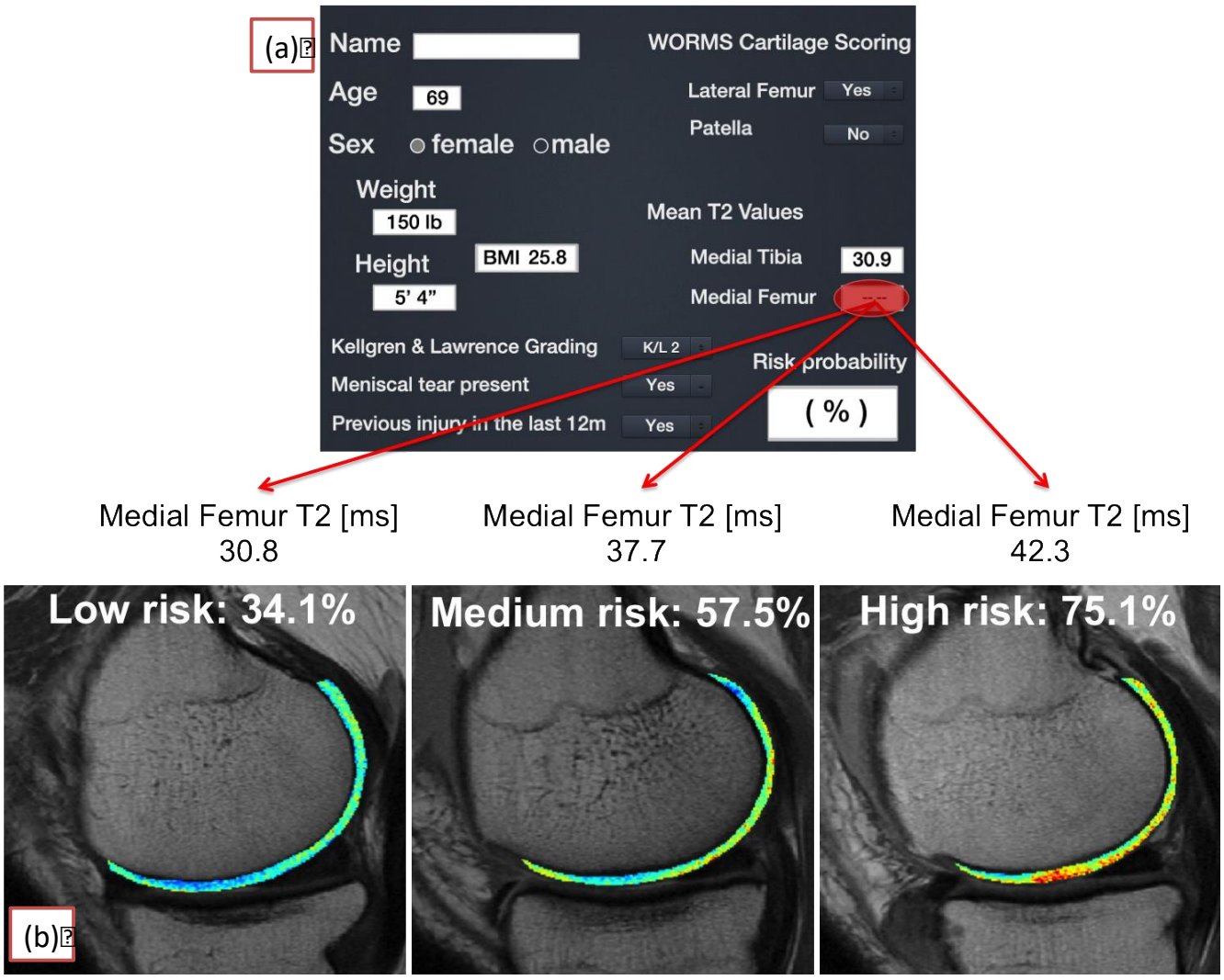
Similar to the FRAX tool, which predicts fracture risk in patients with osteopenia, a tool to predict advanced/endstage OA can also be developed by using a combination of clinical and MRI-based measures. This would allow the implementation of preventative measures at early stages of the disease.

Joseph et al. developed a risk prediction tool for moderate-severe OA (TOARP) over 8 years based on subject characteristics, knee radiographs, and MRI data at baseline using data from the Osteoarthritis Initiative (OAI) (61). They selected 641 subjects with no/mild radiographic OA (Kellgren-Lawrence [KL] 0-2) and no clinically significant symptoms (Western Ontario and McMaster Universities Arthritis Index [WOMAC] 0-1) at baseline. Compartment-specific cartilage and meniscus morphology and cartilage T_2 were assessed. Baseline subject demographics, risk factors, KL score, cartilage WORMS score, presence of meniscus tear, and cartilage T_2 were used to predict the development of moderate/severe OA (KL = 3-4 or WOMAC pain >/=5 or total knee replacement [TKR]) over 8 years. Best subsets variable selection followed by cross-validation were used to assess which combinations of variables best predict moderate/severe OA.

Model 1 included KL score, previous knee injury in the last 12 months, age, gender, and BMI. Model 2 included all variables in Model 1 plus presence of cartilage defects in the lateral femur and patella, and presence of a meniscal tear. Model 3 included all variables in Models 1 and 2, plus cartilage T_2 in the medial tibia and medial femur. Compared to Model 1 (cross-validated AUC = 0.67), Model 3 performed significantly better (AUC = 0.72, P = 0.04), while Model 2 showed a statistical trend (AUC = 0.71, P = 0.08).

A risk calculator for the development of moderate/severe knee OA over 8 years was established that included radiographic and MRI data (**Figure 6**). The inclusion of MRI-based morphological abnormalities and cartilage T_2 significantly improved model performance.

Figure 6: (a) A graphic of the Risk Score calculator, (b) An illustration of the effects of cartilage T_2 on OA risk prediction, while keeping the subject characteristics including KL and WORMS scores constant. As cartilage T_2 increases, the risk for OA development increases, as illustrated by the red areas in the "high risk" T_2 map.



4. Assessment Procedures:

To conform to this Profile, participating staff and equipment ("Actors") shall support each activity assigned to them in **Table 1**.

To support an activity, the actor shall conform to the requirements (indicated by "shall language") listed in the specifications table of the activity subsection in Section 3.

Although most of the requirements described in Section 3 can be assessed for conformance by direct observation, some of the performance-oriented requirements cannot, in which case the requirement will reference an assessment procedure in a subsection here in Section 4.

Formal claims of conformance by the organization responsible for an Actor shall be in the form of a published QIBA Conformance Statement. Vendors publishing a QIBA Conformance Statement shall provide a set of "Model-specific Parameters" (as shown in Appendix D) describing how their product was configured to achieve conformance. Vendors shall also provide access or describe the characteristics of the test set used for conformance testing.

4.1. Assessment Procedures: $T_{1\rho}$ and T_2 of Cartilage

This procedure can be used by a vendor, physicist, or an imaging site to assess the cartilage $T_{1\rho}$ and T_2 using MRI. For $T_{1\rho}$ and T_2 use as quantitative imaging biomarkers of cartilage quality, it is essential to ensure quality assurance of the acquisition and image processing methodology.

For $T_{1\rho}$ and T_2 MR image acquisition, it is important to consider the availability of:

- Appropriate imaging equipment
- Experienced MR technologists for the imaging procedure
- Procedures to ensure standardized image analysis techniques

4.1.1 Imaging Equipment

As outlined in Section 3.2, installation and initial functional validation shall be performed according to manufacturer-defined procedures and specifications. These include specific guidelines on the MRI scanner including coils, sequences and calibration phantom. The recommended field strength is 3 Tesla. It should be noted that relaxation times are field dependent and that field strength should not be changed during longitudinal examinations.
The scanner must be under quality assurance and quality control processes as outlined by local institution and vendor requirements. The scanner software version should be identified and tracked across time.

Periodic QA procedures should be performed once monthly using the calibration phantom developed for cartilage quantitative assessment (such as the NIST phantom which is anticipated to be available in 2021) and the ACR phantom.

Parameter	Actor	Requirement
Imaging equipment	Physicist	As outlined in Section 3.2, installation and initial functional validation shall be performed according to manufacturer-defined procedures and specifications. Specific guidelines for the MRI scanner include coils, sequences and calibration phantom. The preferred field strength is 3 Tesla.

4.1.2 Imaging Procedure

MR technologists or other site personnel performing $T_{1\rho}$ and T_2 MR image acquisition should be MR-certified according to site-specific local or institutional requirements. These individuals should be trained or have prior experience in conducting $T_{1\rho}$ and T_2 MR image acquisition as outlined in Section 3.6. A standard imaging phantom for standardized image acquisition and processing procedures is required but to date such an imaging phantom is not available (work in progress).

Parameter	Actor	Requirement
Imaging procedure	Technologist/ MRI operator	MR technologists or other site personnel performing $T_{1\rho}$ and T_2 MR image acquisition should be MR-certified according to site-specific local or institutional requirements. These individuals should be trained or have prior experience in conducting $T_{1\rho}$ and T_2 MR image acquisition as outlined in Section 3.6. A standard imaging phantom for standardized image acquisition and processing procedures is required.

4.1.3 Imaging Analysis

To date image analysis software is not standardized across vendors, however, artificial/machine learning based algorithms are currently developed for cartilage segmentation and may eventually facilitate and standardize image analysis across sites and vendors. The cartilage segmentation obtained in high resolution gradient echo sequences will be overlaid to the first echo of the $T_{1\rho}$ and T_2 maps (see 3.7). Mean and standard deviation of $T_{1\rho}$ and T_2 values will be calculated in standardized compartments (patella, trochlea, medial and lateral femur and tibia, global knee) (see 3.7).

Compartments may be subsegmented (e.g. deep and superficial layer) and texture analysis may be performed. Note, however, that if smaller regions of interest are used appropriate (and increased) spatial resolution may be required and and reproducibility needs to be in conformance with claims.

4.2. Test-Retest Conformance Study

Actors will demonstrate conformance to the profile through a test-retest repeatability study which will be performed in phantoms and a group of healthy volunteers. The specific situations in which it is required to assess conformity include:

1. Vendor software upgrades for sequences
2. New knee coils.

These requirements apply to a specific site. Similar repeatability studies are required for cross-calibration across different sites. An important assumption underlying the claim is that the image analysis software has a within-subject test-retest coefficient of variation (wCV) of 4-5% (or percent repeatability coefficient (RC) of 11-14%). In order to test this assumption, N=20 patients with early stage disease (KL 0-2) or volunteers will be imaged, with each subject imaged twice on the same day (and additionally, some of these subjects may return for a third scan within one week).

Subject selection and handling should be performed as outlined in Section 3.4 and 3.5. Following the $T_{1\rho}$ and T_2 acquisition on day 1, subjects will be asked to be off the scan table and are repositioned for a second $T_{1\rho}$ and T_2 exam. A third $T_{1\rho}$ and T_2 exam should be performed within 7 days. The data is reconstructed and analyzed using the techniques outlined in Section 3.7.

For each case, calculate the $T_{1\rho}$ (and T_2) for the first replicate measurement (denoted Y_{i1}) and for the second replicate measurement (Y_{i2}) where *i* denotes the *i*-th case. For each case, calculate: $d_i = [(Y_{i1} - Y_{i2})/\{(Y_{i1} + Y_{i2})/2\}] \times 100$. Calculate: $wCV = \sqrt{\sum_{i=1}^{N} d_i^2 /(2 \times N)}$, where N=20. Construct the 95% CI for wCV. If the upper bound <5%, then conformance has been met.

References

1. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann Rheum Dis. 2001;60(2):91-7.
2. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clinics in geriatric medicine. 2010;26(3):355-69.
3. Kim J, Mamoto K, Lartey R, Xu K, Nakamura K, Shin W, et al. Multi-vendor multi-site T1rho and T2 quantification of knee cartilage. Osteoarthritis Cartilage. 2020;28(12):1539-50.
4. Li X, Pedoia V, Kumar D, Rivoire J, Wyatt C, Lansdown D, et al. Cartilage T1rho and T2 relaxation times: longitudinal reproducibility and variations using different coils, MR systems and sites. Osteoarthritis Cartilage. 2015;23(12):2214-23.
5. Luke AC, Stehling C, Stahl R, Li X, Kay T, Takamoto S, et al. High-field magnetic resonance imaging assessment of articular cartilage before and after marathon running: does long-distance running lead to cartilage damage? Am J Sports Med. 2010;38(11):2273-80.
6. Gersing AS, Schwaiger BJ, Nevitt MC, Zarnowski J, Joseph GB, Feuerriegel G, et al. Weight loss regimen in obese and overweight individuals is associated with reduced cartilage degeneration: 96-month data from the Osteoarthritis Initiative. Osteoarthritis Cartilage. 2019;27(6):863-70.
7. Gersing AS, Solka M, Joseph GB, Schwaiger BJ, Heilmeier U, Feuerriegel G, et al. Progression of cartilage degeneration and clinical symptoms in obese and overweight individuals is dependent on the amount of weight loss: 48-month data from the Osteoarthritis Initiative. Osteoarthritis Cartilage. 2016;24(7):1126-34.
8. Aigner T, Gluckert K, von der Mark K. Activation of fibrillar collagen synthesis and phenotypic modulation of chondrocytes in early human osteoarthritic cartilage lesions. Osteoarthritis Cartilage. 1997;5(3):183-9.
9. Stehling C, Baum T, Mueller-Hoecker C, Liebl H, Carballido-Gamio J, Joseph GB, et al. A novel fast knee cartilage segmentation technique for T2 measurements at MR imaging--data from the Osteoarthritis Initiative. Osteoarthritis Cartilage. 2011;19(8):984-9.
10. Pedoia V, Lee J, Norman B, Link TM, Majumdar S. Diagnosing osteoarthritis from T2 maps using deep learning: an analysis of the entire Osteoarthritis Initiative baseline cohort. Osteoarthritis Cartilage. 2019;27(7):1002-10.
11. Bashir A, Gray ML, Hartke J, Burstein D. Nondestructive imaging of human cartilage glycosaminoglycan concentration by MRI. Magn Reson Med. 1999;41(5):857-65.
12. Li X, Majumdar S. Quantitative MRI of articular cartilage and its clinical applications. J Magn Reson Imaging. 2013;38(5):991-1008.
13. Shapiro EM, Borthakur A, Gougoutas A, Reddy R. 23Na MRI accurately measures fixed charge density in articular cartilage. Magn Reson Med. 2002;47(2):284-91.
14. Ling W, Regatte RR, Navon G, Jerschow A. Assessment of glycosaminoglycan concentration in vivo by chemical exchange-dependent saturation transfer (gagCEST). Proc Natl Acad Sci U S A. 2008;105(7):2266-70.

15. Watkins LE, Rubin EB, Mazzoli V, Uhlrich SD, Desai AD, Black M, et al. Rapid volumetric gagCEST imaging of knee articular cartilage at 3 T: evaluation of improved dynamic range and an osteoarthritic population. NMR Biomed. 2020;33(8):e4310.
16. Roemer F, Felson DT, Stefanik JJ, Rabasa G, Wang N, Crema MD, et al., editors. KELLGREN AND LAWRENCE GRADE 2 AND 3 KNEES EXHIBIT A HETEROGENEOUS SPECTRUM OF CARTILAGE DAMAGE: THE MOST STUDY. OARSI; 2021; Virtual
17. Schneider E, Nessaiver M. The Osteoarthritis Initiative (OAI) magnetic resonance imaging quality assurance update. Osteoarthritis Cartilage. 2013;21(1):110-6.
18. Schneider E, NessAiver M, White D, Purdy D, Martin L, Fanella L, et al. The osteoarthritis initiative (OAI) magnetic resonance imaging quality assurance methods and results. Osteoarthritis Cartilage. 2008;16(9):994-1004.
19. Dardzinski BJ, Schneider E. Radiofrequency (RF) coil impacts the value and reproducibility of cartilage spin-spin (T2) relaxation time measurements. Osteoarthritis Cartilage. 2013;21(5):710-20.
20. Bottomley PA, Foster TH, Argersinger RE, Pfeifer LM. A review of normal tissue hydrogen NMR relaxation times and relaxation mechanisms from 1-100 MHz: dependence on tissue type, NMR frequency, temperature, species, excision, and age. Med Phys. 1984;11(4):425-48.
21. Lerski RA, de Certaines JD. Performance assessment and quality control in MRI by Eurospin test objects and protocols. Magn Reson Imaging. 1993;11(6):817-33.
22. Gore JC, Brown MS, Zhong J, Mueller KF, Good W. NMR relaxation of water in hydrogel polymers: a model for tissue. Magn Reson Med. 1989;9(3):325-32.
23. Hardy PA, Li X. Temperature Dependence of T1, T2 and T1rho in Agarose Phantoms. . Joint AAPM/Comp; Virtual 2020.
24. Ammer K. Temperature of the human knee - A review. Thermology International 2012;22(4):137-51.
25. Jungmann PM, Kraus MS, Nardo L, Liebl H, Alizai H, Joseph GB, et al. T(2) relaxation time measurements are limited in monitoring progression, once advanced cartilage defects at the knee occur: longitudinal data from the osteoarthritis initiative. J Magn Reson Imaging. 2013;38(6):1415-24.
26. Serebrakian AT, Poulos T, Liebl H, Joseph GB, Lai A, Nevitt MC, et al. Weight loss over 48 months is associated with reduced progression of cartilage T2 relaxation time values: data from the osteoarthritis initiative. J Magn Reson Imaging. 2015;41(5):1272-80.
27. Lin W, Alizai H, Joseph GB, Srikhum W, Nevitt MC, Lynch JA, et al. Physical activity in relation to knee cartilage T2 progression measured with 3 T MRI over a period of 4 years: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage. 2013;21(10):1558-66.
28. Stehling C, Liebl H, Krug R, Lane NE, Nevitt MC, Lynch J, et al. Patellar cartilage: T2 values and morphologic abnormalities at 3.0-T MR imaging in relation to physical activity in asymptomatic subjects from the osteoarthritis initiative. Radiology. 2010;254(2):509-20.
29. Mosher TJ, Smith HE, Collins C, Liu Y, Hancy J, Dardzinski BJ, et al. Change in knee cartilage T2 at MR imaging after running: a feasibility study. Radiology. 2005;234(1):245-9.
30. Taylor KA, Collins AT, Heckelman LN, Kim SY, Utturkar GM, Spritzer CE, et al. Activities of daily living influence tibial cartilage T1rho relaxation times. J Biomech. 2019;82:228-33.
31. Li X, Han ET, Busse RF, Majumdar S. In vivo T(1rho) mapping in cartilage using 3D magnetization-prepared angle-modulated partitioned k-space spoiled gradient echo snapshots (3D MAPSS). Magn Reson Med. 2008;59(2):298-307.
32. Dixon WT, Oshinski JN, Trudeau JD, Arnold BC, Pettigrew RI. Myocardial suppression in vivo by spin locking with composite pulses. Magn Reson Med. 1996;36(1):90-4.
33. Charagundla SR, Borthakur A, Leigh JS, Reddy R. Artifacts in T(1rho)-weighted imaging: correction with a self-compensating spin-locking pulse. J Magn Reson. 2003;162(1):113-21.
34. Wirth W, Nevitt M, Hellio Le Graverand MP, Benichou O, Dreher D, Davies RY, et al. Sensitivity to change of cartilage morphometry using coronal FLASH, sagittal DESS, and coronal MPR DESS

protocols--comparative data from the Osteoarthritis Initiative (OAI). Osteoarthritis Cartilage. 2010;18(4):547-54.
35. Chen CA, Kijowski R, Shapiro LM, Tuite MJ, Davis KW, Klaers JL, et al. Cartilage morphology at 3.0T: assessment of three-dimensional magnetic resonance imaging techniques. J Magn Reson Imaging. 2010;32(1):173-83.
36. Balamoody S, Williams TG, Wolstenholme C, Waterton JC, Bowes M, Hodgson R, et al. Magnetic resonance transverse relaxation time T2 of knee cartilage in osteoarthritis at 3-T: a cross-sectional multicentre, multivendor reproducibility study. Skeletal Radiol. 2013;42(4):511-20.
37. Maier CF, Tan SG, Hariharan H, Potter HG. T2 quantitation of articular cartilage at 1.5 T. J Magn Reson Imaging. 2003;17(3):358-64.
38. Peterfy CG, Schneider E, Nevitt M. The osteoarthritis initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. Osteoarthritis Cartilage. 2008;16(12):1433-41.
39. Joseph GB, McCulloch CE, Nevitt MC, Heilmeier U, Nardo L, Lynch JA, et al. A reference database of cartilage 3 T MRI T2 values in knees without diagnostic evidence of cartilage degeneration: data from the osteoarthritis initiative. Osteoarthritis Cartilage. 2015;23(6):897-905.
40. Sveinsson B, Chaudhari AS, Gold GE, Hargreaves BA. A simple analytic method for estimating T2 in the knee from DESS. Magn Reson Imaging. 2017;38:63-70.
41. Jordan CD, McWalter EJ, Monu UD, Watkins RD, Chen W, Bangerter NK, et al. Variability of CubeQuant T1rho, quantitative DESS T2, and cones sodium MRI in knee cartilage. Osteoarthritis Cartilage. 2014;22(10):1559-67.
42. Eckstein F, Ateshian G, Burgkart R, Burstein D, Cicuttini F, Dardzinski B, et al. Proposal for a nomenclature for magnetic resonance imaging based measures of articular cartilage in osteoarthritis. Osteoarthritis Cartilage. 2006;14(10):974-83.
43. Pedoia V, Su F, Amano K, Li Q, McCulloch CE, Souza RB, et al. Analysis of the articular cartilage T1rho and T2 relaxation times changes after ACL reconstruction in injured and contralateral knees and relationships with bone shape. J Orthop Res. 2017;35(3):707-17.
44. Kretzschmar M, Nevitt MC, Schwaiger BJ, Joseph GB, McCulloch CE, Link TM. Spatial distribution and temporal progression of T2 relaxation time values in knee cartilage prior to the onset of cartilage lesions - data from the Osteoarthritis Initiative (OAI). Osteoarthritis Cartilage. 2019;27(5):737-45.
45. Hunter DJ, Guermazi A, Lo GH, Grainger AJ, Conaghan PG, Boudreau RM, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage. 2011;19(8):990-1002.
46. Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage. 2004;12(3):177-90.
47. Liebl H, Joseph G, Nevitt MC, Singh N, Heilmeier U, Subburaj K, et al. Early T2 changes predict onset of radiographic knee osteoarthritis: data from the osteoarthritis initiative. Ann Rheum Dis. 2015;74(7):1353-9.
48. Koff MF, Amrami KK, Felmlee JP, Kaufman KR. Bias of cartilage T2 values related to method of calculation. Magn Reson Imaging. 2008;26(9):1236-43.
49. Raya JG, Dietrich O, Horng A, Weber J, Reiser MF, Glaser C. T2 measurement in articular cartilage: impact of the fitting method on accuracy and precision at low SNR. Magn Reson Med. 2010;63(1):181-93.
50. Hardy PA, Andersen AH. Calculating T2 in images from a phased array receiver. Magn Reson Med. 2009;61(4):962-9.
51. Pedoia V, Majumdar S, Link TM. Segmentation of joint and musculoskeletal tissue in the study of arthritis. MAGMA. 2016;29(2):207-21.
52. Gaj S, Yang M, Nakamura K, Li X. Automated cartilage and meniscus segmentation of knee MRI with conditional generative adversarial networks. Magn Reson Med. 2020;84(1):437-49.

53. Liu F, Zhou Z, Jang H, Samsonov A, Zhao G, Kijowski R. Deep convolutional neural network and 3D deformable approach for tissue segmentation in musculoskeletal magnetic resonance imaging. Magn Reson Med. 2018;79(4):2379-91.
54. Norman B, Pedoia V, Majumdar S. Use of 2D U-Net Convolutional Neural Networks for Automated Cartilage and Meniscus Segmentation of Knee MR Imaging Data to Determine Relaxometry and Morphometry. Radiology. 2018;288(1):177-85.
55. Li X, Cheng J, Lin K, Saadat E, Bolbos RI, Jobke B, et al. Quantitative MRI using T1rho and T2 in human osteoarthritic cartilage specimens: correlation with biochemical measurements and histology. Magn Reson Imaging. 2011;29(3):324-34.
56. Shao H, Pauli C, Li S, Ma Y, Tadros AS, Kavanaugh A, et al. Magic angle effect plays a major role in both T1rho and T2 relaxation in articular cartilage. Osteoarthritis Cartilage. 2017;25(12):2022-30.
57. Wang N, Xia Y. Anisotropic analysis of multi-component T2 and T1rho relaxations in achilles tendon by NMR spectroscopy and microscopic MRI. J Magn Reson Imaging. 2013;38(3):625-33.
58. Akella SV, Regatte RR, Wheaton AJ, Borthakur A, Reddy R. Reduction of residual dipolar interaction in cartilage by spin-lock technique. Magn Reson Med. 2004;52(5):1103-9.
59. Joseph GB, Baum T, Carballido-Gamio J, Nardo L, Virayavanich W, Alizai H, et al. Texture analysis of cartilage T2 maps: individuals with risk factors for OA have higher and more heterogeneous knee cartilage MR T2 compared to normal controls--data from the osteoarthritis initiative. Arthritis Res Ther. 2011;13(5):R153.
60. Kundu S, Ashinsky BG, Bouhrara M, Dam EB, Demehri S, Shifat ERM, et al. Enabling early detection of osteoarthritis from presymptomatic cartilage texture maps via transport-based learning. Proc Natl Acad Sci U S A. 2020;117(40):24709-19.
61. Joseph GB, McCulloch CE, Nevitt MC, Gersing AS, Schwaiger BJ, Kretzschmar M, et al. Medial femur T2 Z-scores predict the probability of knee structural worsening over 4-8 years: Data from the osteoarthritis initiative. J Magn Reson Imaging. 2017;46(4):1128-36.

Appendices

Appendix A: Acknowledgements and Attributions

Appendix B: Background Information

References:

Studies supporting Claim 1

1. Atkinson HF et al. MRI T2 and T1ρ relaxation in patients at risk for knee osteoarthritis: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2019;20(1):182. doi:10.1186/s12891-019-2547-7
2. Jordan CD, McWalter EJ, Monu UD, et al. Variability of CubeQuant T1ρ, quantitative DESS T2, and cones sodium MRI in knee cartilage. Osteoarthritis Cartilage 2014;22:1559–1567
3. Kim J, Mamoto K, Lartey R, Xu K, Winalski CS, Tanaka M, et al. Multi-vendor multi-site T1ρ and T2 quantification of knee cartilage. Osteoarthritis and Cartilage. Dec 2020 28(12), 1539-1550.
4. Li X, Pedoia V, Kumar D, Rivoire J, Wyatt C, Lansdown D, Amano K, Okazaki N, Savic D, Koff MF, Felmlee J, Williams SL, Majumdar S. Cartilage T1ρ and T2 relaxation times: longitudinal reproducibility and variations using different coils, MR systems and sites. Osteoarthritis Cartilage. 2015 Dec;23(12):2214-2223.
5. Li X, Wyatt C, Rivoire J, Han E, Chen W, Schooler J, Liang F, Shet K, Souza R, Majumdar S. Simultaneous acquisition of T1ρ and T2 quantification in knee cartilage: repeatability and diurnal variation. J Magn Reson Imaging. 2014 May;39(5):1287-93
6. MacKay JW et al. Systematic review and meta-analysis of the reliability and discriminative validity of cartilage compositional MRI in knee osteoarthritis. Osteoarthritis Cartilage. 2018;26(9):1140-1152. doi: 10.1016/j.joca.2017.11.018.
7. Schneider E, Nessaiver M. The Osteoarthritis Initiative (OAI) magnetic resonance imaging quality assurance update. Osteoarthritis Cartilage. 2013 Jan;21(1):110-6

Appendix C: Conventions and Definitions

C.1 List of Abbreviations

- ACL anterior cruciate ligament
- ACR American College of Radiology
- AF Arthritis Foundation
- AUC Area under the curve
- BMD bone mineral density
- C2P site-to-site collaboration
- cLF central lateral femur
- cMF central medial femur
- CV coefficient of variation
- DESS Double Echo Steady State
- dGEMRIC delayed Gadolinium MRI of Cartilage
- FFE Fast Field Echo
- FLASH Fast low angle shot
- FRAX Fracture Risk Assessment Tool
- gagCEST chemical exchange saturation transfer imaging of glycosaminoglycans
- Gd-DTPA: Gadolinium-diethylene triamine pentaacetic acid
- JSN joint space narrowing
- KL Kellgren-Lawrence
- LF lateral femur
- LT lateral tibia
- MAPSS magnetization-prepared angle-modulated partitioned k-space spoiled gradient echo snapshots
- MENSA Multi-Echo iN Steady-state Acquisition
- MSME Multi-spin multi-echo
- mFTJ medial femoro-tibial joint compartment
- MLEV Malcolm Levitt's
- MT medial tibia
- NIST National Institute of Standards and Technology
- OA osteoarthritis
- OAI Osteoarhritis Initiative
- P Patella
- pLF posterior lateral femur
- pMF posterior medial femur
- QA quality assurance
- RC repeatability coefficient
- RF radiofrequency
- RMS root mean squared
- SAR Specific Absorption Rate
- SD Standard Deviation
- SNR Signal-to-Noise Ratio
- SPGR Spoiled Gradient Recalled
- T/R Transmit-Receive
- TE echo time

- TR repetition time
- TrF/T Trochlea
- VPS views per segmentation
- WOMAC Western Ontario and McMasters University Osteoarthritis Index
- WORMS Whole-organ Magnetic Resonance Imaging Score

Appendix D: Detailed imaging protocols

See 3.6.2

Appendix E: Checklists

E.1-3. Checklist Site / Periodic QA/ Staff qualification

Parameter	Conform (y/n)	Requirement	Site option
Site Qualification (Section 3.2)			
Qualification activities	□ Yes □ No	Shall perform qualification activities for MRI scanner, Scanner Operator, and Image Analyst to meet equipment (hardware and software), acquisition and image analysis required to achieve the claims	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:
Periodic QA (Section 3.3)			
Periodic QA	□ Yes □ No	Shall perform calibration monthly using $T_{1\rho}$/T_2 and ACR phantom. Shall record the date/time of the calibration for auditing.	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:
Staff qualification (Section 3.1)			
Qualification	□ Yes □ No	Shall undergo documented training by qualified physicist/radiologist in understanding key acquisition principles of the cartilage $T_{1\rho}$ and T_2 images as well patient positioning. Training by a qualified radiologist shall also include image analysis with regards to anatomical location and selection of measurement target..	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:

E.4-5 Subject selection and handling/ Radiologist and Technologist

Parameter	Conform (y/n)	Requirement	Site option
Subject selection (Section 3.4)			
Clinical findings	□ Yes □ No	Needs to know limitations and indications of $T_{1\rho}$ and T_2 measurements. Only patients without significant cartilage loss (KL 0-2) decided by clinician and/or radiologist	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:
Subject handling (Section 3.5)			
Patient handling	□ Yes □ No	Patient shall rest 30 minutes before the scans and not have performed strenuous exercise within 48 hours of the exam.	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:

1055

E.6. Image data acquisition/ Scanner Operator Checklist

Parameter	Conform (y/n)	Requirement	Site option
Image data acquisition (3.6.)			
Protocol	□ Yes □ No	Shall check that implemented scan protocol parameters comply with the scan protocol requirements as detailed in the profile specifications in 3.6.2	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:
Patient positioning	□ Yes □ No	In order to achieve reproducible images positioning shall be standardized. Ankles and legs shall be sandbagged during MRI scan to avoid motion in patients/volunteers. Subject-specific landmark shall be centered on the knee, which shall be located as close as is feasible to magnet isocenter.	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:
Scan parameters	□ Yes □ No	Subject-specific adjustments within allowed parameter ranges (Table 3.6.2) shall be made to suit body habitus. Parameter adjustments for a given subject shall be constant for serial scans.	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:
Acquisition hardware	□ Yes □ No	The same scanner and coil shall be used for baseline measurement and a subsequent longitudinal measurement for detecting change in $T_{1\rho}$ and T_2.	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:
Image data reconstruction	□ Yes □ No	Standard image data reconstruction	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:
Image distribution	□ Yes □ No	From the scanner to workstations for image analysis Patient confidentiality rules will apply	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:

E.7. Image Analysis Checklist/ Image Analyst

Parameter	Conform (y/n)	Requirement	Site option
Image analysis (3.7.)			
Cartilage segmentation	□ Yes □ No	Cartilage shall be segmented on high-resolution gradient echo images. Segmentations will be registered to the first echo of the $T_{1\rho}$-weighted images. Semi-automatic or automatic segmentation software shall be used.	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:
Compartments	□ Yes □ No	Seven compartments shall be defined: patella (P), trochlea (TrF), lateral and medial femoral condyles (LF and MF), lateral and medial tibiae (LT and MT) and global knee cartilage. The LF/MF can be further divided into sub-compartments, deep and superficial layers may also be examined separately	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:
Lesions	□ Yes □ No	Lesion specific analysis: Regions of interest shall be manually drawn around the lesion area in all slices. Control region: The segmentation of the "surrounding" cartilage will include all the remaining clearly distinguishable cartilage of the articular plate.	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:
T1ρ and T2 maps	□ Yes □ No	The $T_{1\rho}$ and T_2 maps shall be reconstructed pixel-by-pixel by fitting the $T_{1\rho}$- and T_2-weighted images based on equations $S(TSL) = S_0 \exp(-TSL/T_{1\rho})$ and $S(TE) = S_0 \exp(-TE/T_2)$, respectively.	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:

1065

E.8. Image Interpretation / Radiologist

Parameter	Conform (y/n)	Requirement	Site option
Image interpretation (3.8.)			
	□ Yes □ No	Longitudinal change according to claims.	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:

1070