QIBA Profile: MR-based cartilage compositional biomarkers ($T_{1\rho}$, T_2) for risk prediction, early diagnosis and monitoring of treatment of degenerative joint disease

Stage: A. Initial Draft

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Change Log:

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

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

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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.

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Q. Calibration Phantom / Cross calibration
A. Work in progress – Agarose gel phantom sets have been manufactured by the Phantom Lab, however no $T_{1\rho}$ and T_2 reference values are available for the phantoms. XL has a pending NIH R01 on developing 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.

Q. Automated analysis algorithm
A. work in progress – AI algorithm has been developed – needs to be applied

Q. Profile – 10-05-19
      1. Add info about vendors (Xiaojuan)
      2. send to committee members for review and comments
      3. go over protocol with technologists (Thomas)
      4. update dashboard on 100519

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 of degenerative joint disease**. It places requirements on Acquisition Devices, Technologists, Radiologists, Reconstruction Software and Image Analysis Tools involved in Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image 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 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 precision of 11-14%. 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 apply 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).

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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.

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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.

105 • 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.

110 • 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.

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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). 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 have an impact to 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. This biomarker opportunity will allow to enhance development, potentially improve approval and facilitate application in the future.

Cartilage compositional imaging biomarkers allow earlier diagnosis, better prediction and more sensitive monitoring of degenerative joint disease. 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.

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 <u>by all relevant staff and equipment</u> 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%. This claim applies to 3T scanners 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%. This claim applies to 3T scanners 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.

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.

Important considerations and limitations:

- Details of the claim were derived from a review of the literature summarized in Appendix B.
- 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. 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.
- 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.
- 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).
- This Claim is based on semi-automatic or automatic cartilage segmentation using dedicated analysis software.
- 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 intra- and intervendor reproducibility; the manuscript has been submitted to the Journal "Osteoarthritis & Cartilage" (04/2020). A R01 grant (PI: Dr. Xiaojuan Li) has been funded which will allow rigorous reproducibility testing using scanners from the same and different manufacturers; it will also include development of a dedicated calibration phantom (start date is 05/2020).

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: $2.77 \times wCV \times 100$.

175 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 size beyond these limits, you can be 95% confident there has been a true change in the size of the tumor, 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.

180 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.

185 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 (3).

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.
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.

195 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. How study sponsors and others decide to handle deviations for their own purposes is entirely up to them.

3.1. Staff Qualification

200 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

205 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.

210 3.1.2 Specification

Parameter	Actor	Requirement
Qualification	Technologist/ Image Analyst	Shall undergo documented training by qualified physicist/radiolgist 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 (4) (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 are not recommended as reproducibility was found to be limited unless special holders to improve reproducibility are used (unpublished QA data).

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).

A phantom which was used for a previous Arthritis Foundation funded study is currently available at several sites (see reference 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).
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 R01 grant application has been funded with Dr. Xiaojuan Li being the PI (start date 05/2020). Within the framework of this grant Dr. Li will work with NIST Katy Keenan to develop a calibration phantom (with a built-in thermometer and allowing not only quantitative compositional but also geometric measurements) which will be made available for commercial use.

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 quadrature /(minimum) eight-channel phased-array coils
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-Physicist	Calibration phantoms will be used to validate measurements and test reproducibility.
Cartilage segmentation	Image Analysis Tool	Semi-automatic or automatic software that allows segmentation of cartilage with high reproducibility.

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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 (5)) and the ACR phantom. Specific phantom holders need to be used to acquire the images (5-7).

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 and human volunteers. 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 for each study period.

Measurements will be compared to reference sites.

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 (6, 7). 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), image uniformity, spatial accuracy, eddy current, spatial resolution and gradient calibration.

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 (6, 7). Dardzinski et al showed that quadrature transmit/eight-channel phased-array receive coils provided higher SNR compared to quadrature transmit/receive coils (8). 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 (5). 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%

280　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 (4). The mean inter-site inter-vendor CVs in phantoms were 6.45% and 5.23% for $T_{1\rho}$ and
285　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.

It should be noted that phantom T_2 measurements are sensitive to seasonal environmental fluctuations, such as temperature which may not only impact T_2 values but may also impact detection electronics or overall power levels into the various system components. Calibration phantom needs to be stored in scanner room the night before the scan as temperature in scanner room is best controlled. Temperature has a significant impact on relaxation times (Peter Hardy, personal communication and (9)) .

290　**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.

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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

300 Subject selection should 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 (10). This is why only patients with relatively early disease or at least joint compartments with maintained cartilage should be examined.

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

Overall goal is risk assessment and monitoring of interventions/management

305 1. Patients with **early disease** (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 this found in runners or 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.

310 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 (11, 12) (13) and physical activity (3, 14, 15) (16) or pharmacotherapy (limited evidence).

5. $T_{1\rho}$ and T_2 may be used to monitor **cartilage repair** maturation.

315 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.

320   Subjects shall be examined after having rested in a seated position for 30 minutes. Patients should not have exercised on the day of the exam. 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 deemed to result in push-back both by the radiology site and the patient.

In order to achieve reproducible imaging and minimal motion positioning aids such as leg/knee holders or foam cushions and positioning
325   straps shall be used. Ankles and legs shall be sandbagged and and positioning straps shall be used during the 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. 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

330   Subject handling is based on the fact that biomechanical loading may impact $T_{1\rho}$ and T_2 measurements and potentially provide abnormal values which may be either too high (3) or too low (16).

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).
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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).

340   ### 3.5.2 Specification

Parameter	Actor	Requirement
Exam preparation	Technologist	Need to make sure that patient rest 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** (4, 5, 17). The $T_{1\rho}$ preparation pulses contain continuous hard 90_x (tip-down pulses) - spin lock pulses - $90°_{-x}$ (tip-up pulses). Composite tip-up and tip down pulses are applied to improve robustness to B_0 inhomogeneity (18). 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 (19). 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 contained an MLEV (**M**alcolm **Lev**itt's composite-pulse decoupling sequence) train of nonselective composite $90°_x 180°_y 90°_x$ refocusing pulses.
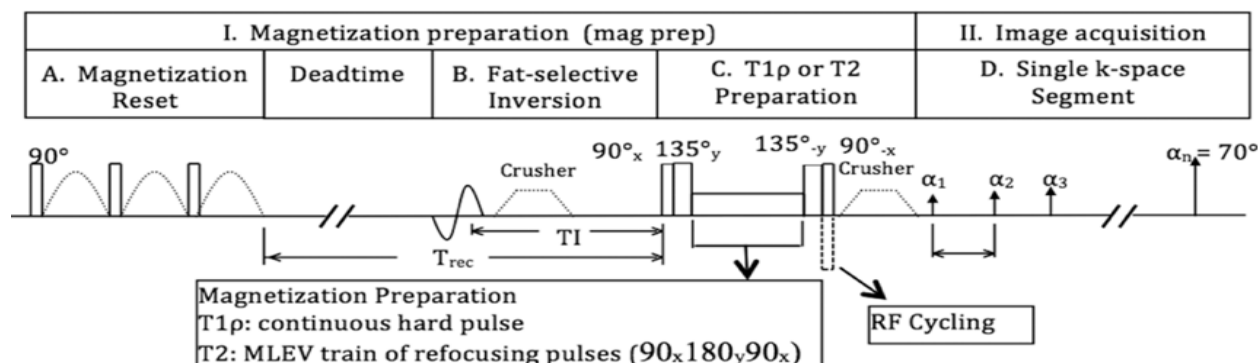

Fig. 1: The MAPSS-based $T_{1\rho}$ and T_2 imaging sequence is available as research prototype by the three major MR vendors including GE, Simens and Philips.

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 (SPGR on GE, FLASH or DESS on Siemens and FFE on Philips) (20).

Parameters for the MAPSS and high resolution gradient echo sequences are provided in Table 1, which should also provide sufficient image quality and signal to noise ratio.

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

3.6.1 Discussion

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 on GE/Siemens) have also been used in the literature for cartilage segmentation (21). In summary based on results of previous work we would recommend Gradient-echo based sequences as standards for segmentation.

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 ranged 5.4 to 10.0 ms (10%~25%) (22). The sequence is also prone to variations introduced by stimulated echoes and magnetization transfer effect (23). In the OAI protocol, the first echo needs to be skipped during T2 fitting in order to minimize the potential bias (24).

3.6.2 Specification

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TABLE 2. SUGGESTED IMAGING PROTOCOL (FOR ALL VENDORS) HIGH RES GRAD ECHO SEQUENCE (4)

Parameter	Actor	Requirement	Dicom Tag
Field Strength	Acquisition Device/ Technologist	3.0T	
Acquisition Sequence		DESS/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	
Time of spin-lock (TSL)/Prepared TE (ms)		n/a	

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TABLE 3. SUGGESTED IMAGING PROTOCOL (FOR ALL VENDORS) 3D $T_{1\rho}$ AND T_2 MAPSS (4)

Parameter	Actor	Requirement	Dicom Tag
Field Strength		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	Acquisition Device/ Technologist	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	

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

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.

425

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.

430

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. Chris Peng (dr.chrispeng@gmail.com) at Albert Einstein College of Medicine and Dr. Can Wu (can.wu@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.

435

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 Simens and IDEA license.

440

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 have 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.

450

3.7. Image Data Analysis

455 **Global and compartment specific analysis:**

Cartilage shall be segmented on high-resolution gradient echo images as previously proposed by Eckstein et al. (25). Six compartments shall be defined: patella (P), trochlea (TrF), lateral and medial femoral condyles (LF and MF), lateral and medial tibiae (LT and MT). The LF/MF and LT/MT can be further divided into sub-compartment 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

460 (26).

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 $S(TE) = S_0 \exp(-TE/ T_2)$, with or without noise components, respectively.

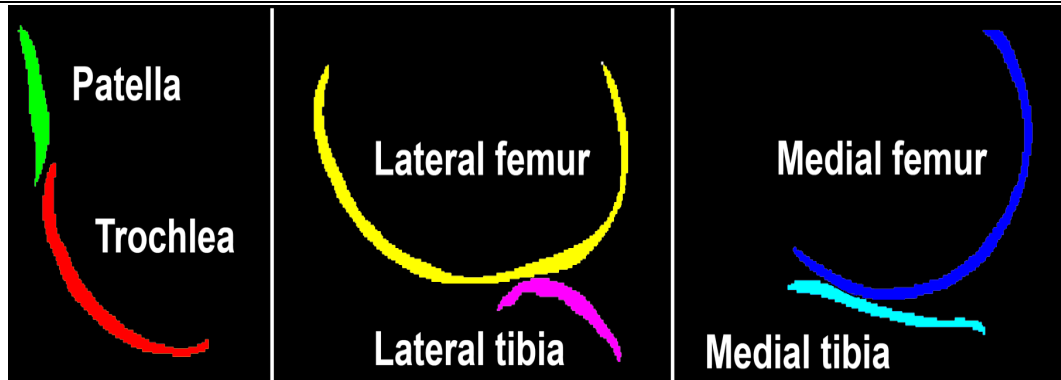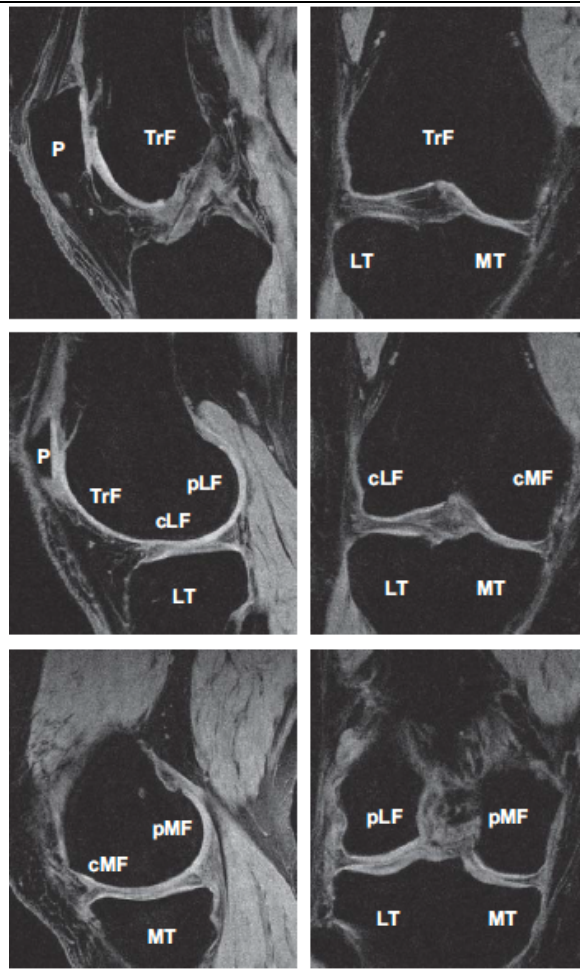465 Semi-automatic or automatic segmentation software shall be be used.

Fig. 2. Cartilage compartments (left) and anatomical lables of knee joint cartilage plates (right) according to reference (25). (P=patella, TrF=trochlea, LT=lateral tibia, MT=medial tibia, 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 (27). 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 (PAT) or trochlea (TRO) (**Fig.3**). Analysis shall take magic angle effects into consideration.
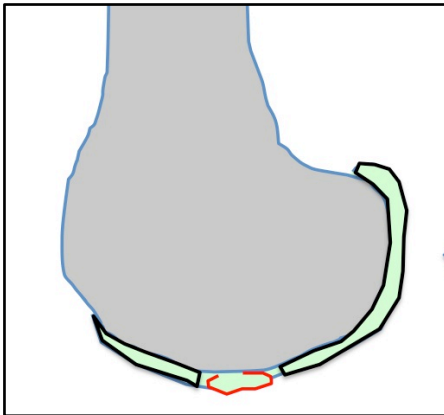
475

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

3.7.1 Discussion

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

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. Piece-wise (separated for each bone) rigid registration or non-rigid registration will be needed to register between the high-resolution anatomical images and 485 $T_{1\rho}$ and T_2 images.

Non-linear fitting is recommended which provides more reliable results compared to linear fitting (28, 29). At least three echoes images are needed for reliable fitting. With more than six echo images, three parameter fitting (with noise components) can provide more reliable fitting results but comes at a cost of longer scan times. 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.

490　There are a large number of publications on cartilage segmentation methods, including manual, semi-automatic and automatic-segmentation methods (30). 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 (31-33). Such automatic segmentation methods are promising for facilitating future clinical translation of advanced quantitiative imaging techniques.

495　**3.7.2 Specification**

Parameter	Actor	Requirement
Global analysis	Technologist/ image analyst	Perform manual, 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

500　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.

505　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
510　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 20-80 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).

515

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 T2 database is available from the Osteoarthritis Inititiative data (24). This gender, age and BMI-specific reference database of cartilage T2 values is based on 481 subjects aged 45-65 years with radiographic Kellgren-Lawrence Scores 0/1 in the study knee. Baseline T2 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 T2. This database demonstrated significant differences in mean cartilage T2 values between joint compartments. Although females had slightly higher T2 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 T2 in all compartments, most pronounced in the patella (3.27% increase in median T2/10 years, $P = 0.009$). Significant associations between BMI and T2 were observed, most pronounced in the lateral tibia (5.33% increase in median T2/5 kg/m(2) increase in BMI, $P < 0.0001$), and medial tibia (4.81% increase in median T2 /5 kg/m(2) increase in BMI, $P < 0.0001$).

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Table 1: Reference database of percentiles of T2 values (in ms) in subjects with compartment-specific cartilage scores of WORMS 0/1 subdivided by gender*

	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 T2 in each joint compartment (with WORMS scores of 0/1). Figure shows adjusted means with 95% confidence intervals.

The Association Between Age and Cartilage T2
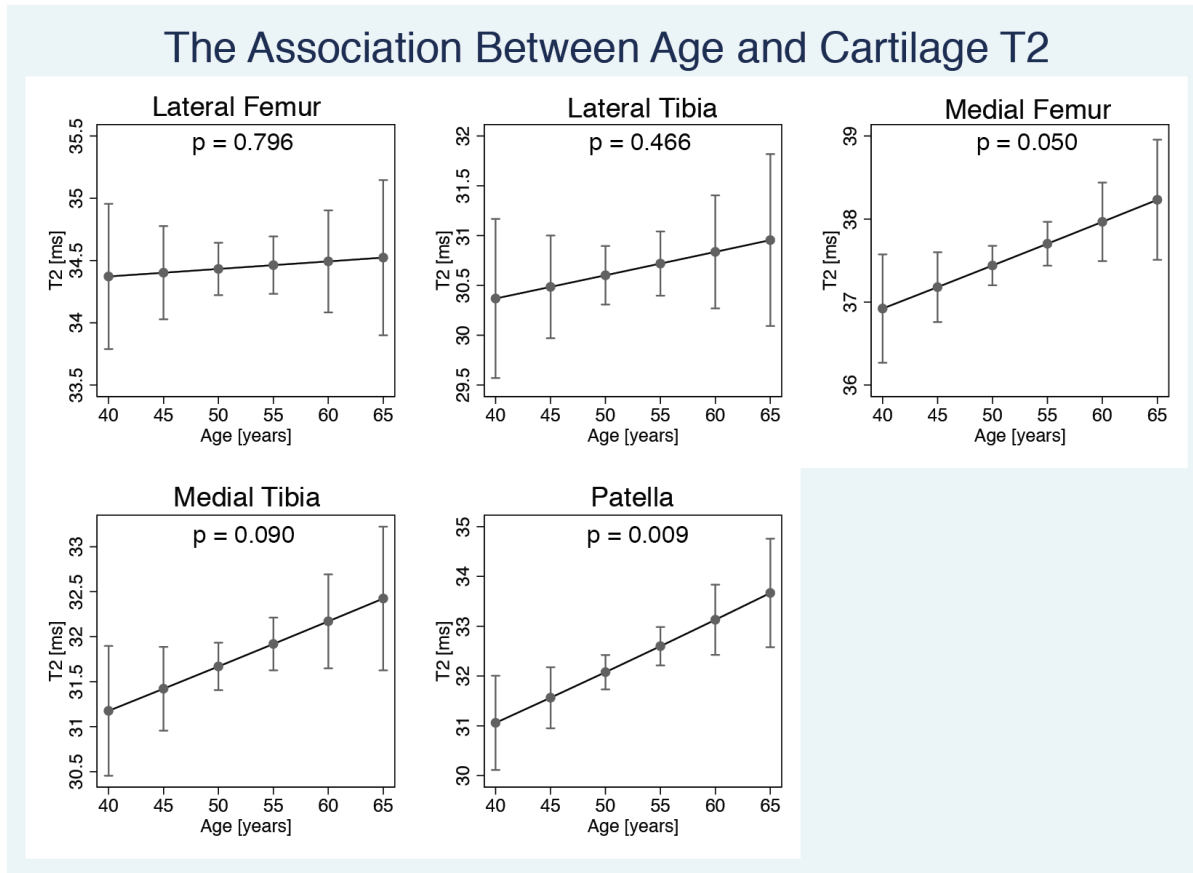
To address standardization issues related to hardware and software Z-scores shall be used; global and compartment specific Z-scores for $T_{1\rho}$ and T_2 values are obtained by calculating the standard deviation compared to healthy reference global or compartment specific cartilage using the equation:

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

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 T2 Z-scores based on the probability of structural worsening of knee cartilage and whole joint degeneration over 4-8 years (34). 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 T2 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. T2 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 T2 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 T2 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 T2 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: The predicted probability of worsening of KL score over 8 years (orange), joint space narrowing (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 T2 Z-score in the medial femur as a predictor. For all outcomes, the probability of incidence/progression increases as a function of cartilage T2 Z-score in the medial femur. The table shows the associated probabilities of incidence/progression based on categorical values of cartilage T2 Z-scores in the medial femur.
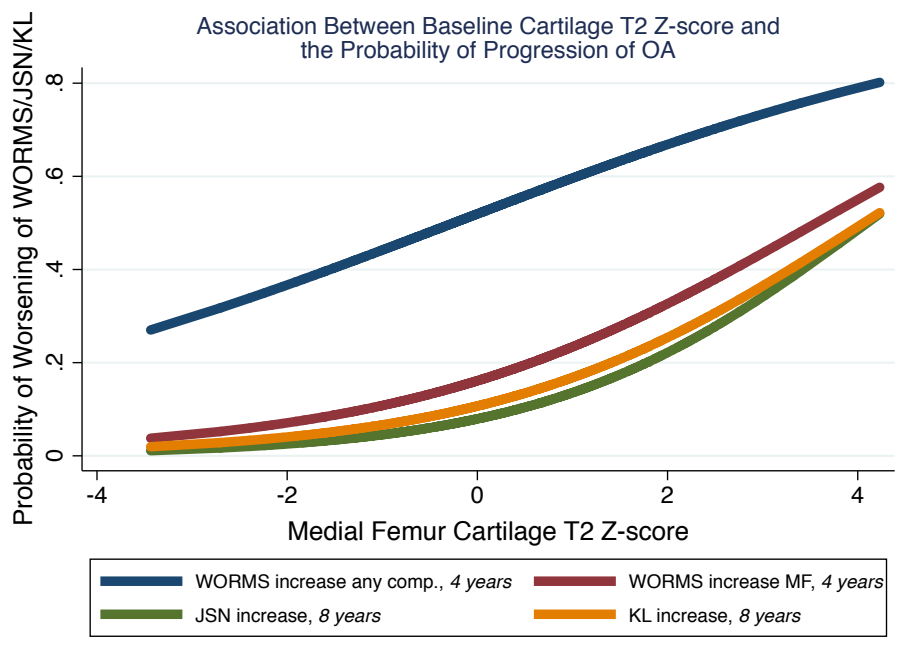
By defining a Z-score of greater 2 as indicating an increased risk of joint degeneration we would eliminate absolute T2 and T1ρ values in data interpretation. We would still need normal reference values for an individual

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 to implement 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) (35). 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 T2 were assessed. Baseline subject demographics, risk factors, KL score, cartilage WORMS score, presence of meniscus tear, and cartilage T2 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 T2 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).

We established a risk calculator for the development of moderate/severe knee OA over 8 years that includes radiographic and MRI data. The inclusion of MRI-based morphological abnormalities and cartilage T2 significantly improved model performance.

Figure 6: (a) A graphic of the Risk Score calculator, (b) An illustration of the effects of cartilage T2 on OA risk prediction, while keeping the subject characteristics including KL and WORMS scores constant. As cartilage T2 increases, the risk for OA development increases, as illustrated by the red areas in the "high risk" T2 map.
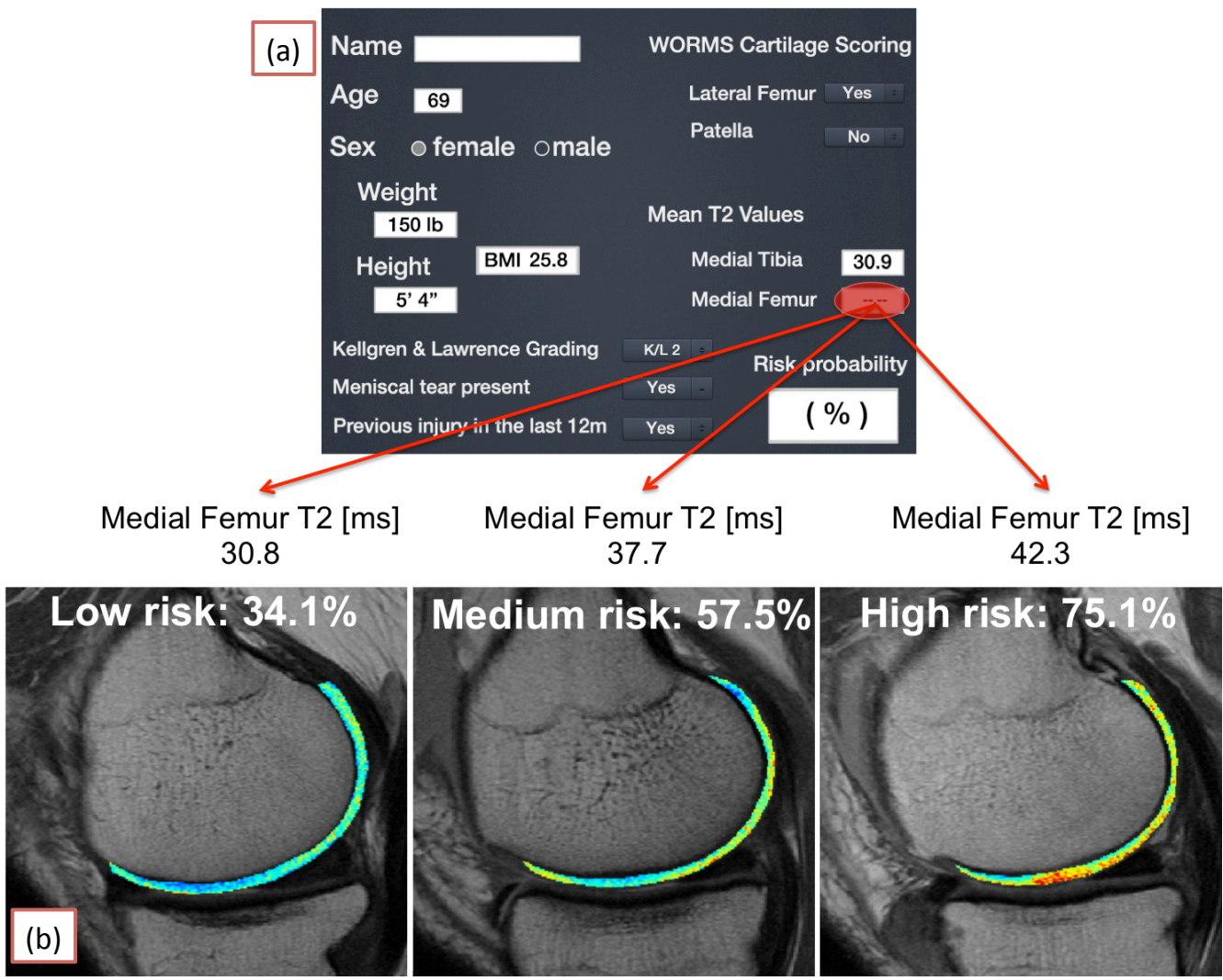
4. Assessment Procedures:

605 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
610 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
615 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 $T_{1\rho}/T_2$ using
620 MRI. For $T_{1\rho}/T_2$ use as a quantitative imaging biomarker of cartilage quality, it is essential to ensure quality assurance of the acquisition and image processing methodology.

For $T_{1\rho}/T_2$ MR image acquisition, it is important to consider the availability of:
- Appropriate imaging equipment
625 - 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
630 manufacturer-defined procedures and specifications. This includes specific guidelines on the MRI scanner including coils, sequences and calibration phantom. The recommended field strength is 3 Tesla.
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.

635 Periodic QA procedures should be performed once monthly using the calibration phantom developed for cartilage quantitative assessment (work in progress Dr. Li) 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 $T_{1\rho}/T_2$ 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 $T_{1\rho}/T_2$ 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 Dr. Li).

Parameter	Actor	Requirement
Imaging procedure	Technologist/ MRI operator	MR technologists or other site personnel performing $T_{1\rho}/T_2$ 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 $T_{1\rho}/T_2$ 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) (see 3.7). Compartments may be subsegmented (deep and superficial layer) and texture analysis may be performed.

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 surface 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=40 normal subjects 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 stand 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_{1p} (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=40. Construct the 95% CI for wCV. If the upper bound <5%, then conformance has been met.

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Appendices

Appendix A: Acknowledgements and Attributions

Appendix B: Background Information

780 **References:**

Studies supporting Claim 1

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Appendix C: Conventions and Definitions

n/a

Appendix D: Detailed imaging protocols

800 See 3.6.2

Appendix E: Checklists

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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/radiolgist 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:

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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:

Parameter	Conform (y/n)	Requirement	Site option
		Subject handling (Section 3.5)	
Patient handling	□ Yes □ No	Patient shall rest 30 minutes before the scans and not have performed strenuous exercise with 48 hours of the exam.	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:

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E.6. Image data acquisition/ Scanner Operator Checklist

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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 standardized 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:

Parameter	Conform (y/n)	Requirement	Site option
Image distribution	□ Yes □ No	From the scanner to workstations for image analysis Patient confidentialty rules will apply	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:

825   *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 gradience 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	Six compartments shall be defined: patella (P), trochlea (TrF), lateral and medial femoral condyles (LF and MF), lateral and medial tibiae (LT and MT). The LF/MF and LT/MT can be further divided into sub-compartments	□ 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 $S(TE) = S_0 \exp(-TE/T_2)$, with or without noise components, respectively.	□ routine, do already □ feasible, will do □ feasible, will not do □ not feasible, explain why:

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:

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