QIBA Musculoskeletal (MSK) Biomarker Committee (BC) Call

Tuesday, April 27, 2021 at 10 a.m. CT

Call Summary

In attendance			**RSNA**
Xiaojuan Li, PhD (Co-Chair)	Ali Guermazi, MD, PhD	Yuxi Pang, PhD	Joe Koudelik
Thomas Link, MD, PhD (Co-Chair)	Youngkyoo Jung, PhD, DABR	Valentina Pedoia, PhD	Susan Stanfa
Angie Botto-van Bemden, PhD	Feliks Kogan, PhD	Qi (Chris) Peng, PhD	
Robert Boutin, MD	Kecheng Liu, PhD, MBA	Fraser Robb, PhD	
Maggie Fung, MEng	Nancy Obuchowski, PhD	Cory Wyatt, PhD	

MSK Profile – Review Public Comments (Dr. Link)

- The public comment period closed on October 29, 2020, and MSK BC members have been using the **MSK public comment resolutions Google Sheet** to document how feedback is addressed

Discussion on unaddressed comments resumed

James Mackay, MBBCHIR, MRCP (Norwich Medical School, UK)

- Because a t-test would not provide sufficient information about the magnitude of any systematic difference between different hardware/software settings, a Bland-Altman analysis was recommended
  - Sites should take measurements for repeatability using a phantom, but methods for quality control/calibration and calculating wCV would differ; for QC, data would be compiled to compute variance and mean to confirm that measurements are consistent
  - wCV should be computed for each vial; Bland-Altman analysis plots would include true value on the x axis and variability on the y axis
    - Variability should not increase as the concentration in the vials increases; it should be constant over the range of true values
    - wCV should not exceed 3%, as indicated in MSK Profile Claims
  - To calculate wCV in her study, Dr. Li used six phantoms consisting of three vial pairs with average composition with different values

- Inclusion of a more defined description was recommended re: what constitutes “exercise” within the context of the recommendation that subjects should not have exercised on the day of the exam
  - It was clarified that subjects should not engage in high-impact exercise, e.g., sports, running, workouts in the gym or any unusual, atypical physical activities such as a marathon or extended hike within 48 hours preceding the MRI

- It was suggested that qDESS sequence, which allows simultaneous acquisition of morphological data and T2 maps should be mentioned in the Profile; a paragraph will be devoted to this topic
- Specifying exclusion thresholds for implausible values (e.g., T2 > 130 msec or T1rho > 150 ms) or poor fits (e.g., r-squared < 0.8) above/below which pixels should be excluded from analysis was recommended
  - 2007 Li, et al. OAC 15;789-797: To reduce artifacts caused by partial volume effects with synovial fluid, regions with relaxation time greater than 150 ms in T1rho or 130 ms in T2 maps were removed by thresholding from the data used for quantification

Dimitrios Karampinos, PhD (Technical University of Munich)

- Clear recommendation needed on whether MAPSS should be the only sequences used for T2 mapping; additional information needed re: the use of alternate sequences, such as Multi echo spin echo sequences (MESE) for cartilage T2 mapping as well

- There have been previous discussions on this topic and the MSK BC resolved to focus on best tested, best reproducibility data; MAPSS is recommended for T2 and T1rho; Alternative sequences for T2 may be considered including MESE T2, and qDESS T2 (additional discussion needed)

- The MSK BC agreed to recommend in the discussion section, the use parallel imaging and compressed sensing for T2/T1rho mapping, using standard parameters and meeting conformance with the profile claims

Feliks Kogan, PhD (Stanford University)

- Disagreement re: discouraging the use of flexible coils as it led to increased SNR and reproducibility
  - MSK BC concern that use of flexible coils may be less rigorous and present difficulty in achieving Claims, but it was also recognized that flexible coils may be needed to accommodate large knees that cannot fit into the knee coil
  - Some MR systems cannot achieve recommended spin-lock frequency (500Hz) with the longest spin-lock time (e.g., 70 or 80ms for the last echo) using flexible coils (i.e., body transmit); in that situation, slightly lower SL frequency (400Hz) and shorter TSL (~50ms) may be used, provided the quantification results meeting conformance with the profile claims

- Discussion on SNR
  - Inclusion of a statement re: minimum image (for long TE) SNR to help guide selection of parameters was suggested
  - Discussion. re: whether to add SNR criteria, as most users may not have enough experience with it
  - Specific image SNR quality needs to be evaluated to verify that T1rho or T2 values are not being inflated
  - Additional MSK BC discussion needed on these topics

- Suggestion to separate discussions of cross-sectional (CS) studies from longitudinal studies in the Profile
  - The MSK BC Claim is longitudinal and additional study is needed before a CS Claim can be included
  - It was noted that there may be variability across different scanners from the same manufacturers
  - CS studies across different sites were referenced, including: *Osteoarthritis Cartilage*. 2015 Dec;23(12):2214-2223, *Osteoarthritis Cartilage*. 2020 Dec;28(12):1539-1550

- As the utility of the quantitative methods in the Profile is largely based around detection of longitudinal changes, it was suggested that a choice of T2/T1rho sequence be provided; this would ensure that intra-subject repeatability is in-line with Claim 1a and 1b (<5% CV) and methods are appropriate markers of T2 and T1rho, respectively
  - Suggestion to include QIBA criteria on alternative imaging methods; this will help to compare images across sites when different sequences or hardware are used
  - Alternative sequences including MESE T2 and qDESS T2 may be considered if they meet the Claims including required longitudinal reproducibility
  - Sequences to be discussed, basing recommendations on reproducibility, validation and SNR
  - New methods that improve speed, accuracy or robustness offer to improve utilization of these methods should be adapted as long as they uphold the standard of repeatability in order to detect longitudinal changes
  - Other sequences have already been added to the Profile and Dr. Link will request information from Dr. Kogan on qDESS for inclusion as well

- It was suggested that CS analysis or z-score potentially have the most clinical utility and discussion is needed re: CS data interpretation
  - The MSK BC resolved that reference databases are not part of QIBA Profiles and are believed to be beyond the scope of the MSK BC Profile
  - Previous studies that describe a reference database for T2 measurements and a risk score are included in the Profile under discussion to provide material for expansion into clinical application

- Imaging 40 normal subjects twice on the same day for test-retest conformance was deemed too high a standard and not realistic/not doable
    - Difficulty balancing practical and statistical issues was cited
    - The number of required subjects depends on the quality of the site and wCV, i.e., if only 10 subjects are scanned but wCV is 2%, it is likely that the Claim was met; if wCV is higher (~9%), additional subjects are needed to prove conformance
    - Once a Profile has advanced to Claim Confirmed (stage 4), a test-retest study is a reasonable and feasible request

T2 Analysis of the Entire Osteoarthritis Initiative Dataset: UCSF/ci^2 center for intelligent imaging (Dr. Pedoia)

- OAI DESS auto segmentation: bone (femur, tibia, patella) and cartilage (femoral, tibial, patellar) encoder-decoder deep learning models were used
- Fully automatic cartilage thickness measurements and those performed manually and publicly available on the OAI website (N=4,299) were compared
- On a single patient basis, strong correlations and mean absolute errors within the voxel resolution were observed
- Thickness Biomarker:
    - All performances were high and there were no significant differences between manual and automatic segmentation
    - Errors in thickness estimations were comparable to image resolution
    - Patella cartilage segmentation was challenging for all methods

- 3,921 MRI images (1,890 unique subjects) were **segmented manually** during several studies performed between 2011 and 2018
- This dataset was used to train and test an automatic model to segment cartilage using MSMS T2 sequence
- Comparable with human inter-personal variability **proving human/machine interchangeability**
- qMRI discovery was that better features extraction for imaging biomarkers are needed
- Single biomarker AUC to predict incident OA and future total knee replacement ranged between 0.745-0.807 with cartilage thickness being the stronger predictor
- The combined model showed significantly higher performance with AUC=0.888

Next Steps

- Changes in response to public comments will be incorporated into the Consensus draft of the MSK Profile
- During the June 22 meeting, a post-resolution BC review process will be discussed
- Reviewing assignments can be divided up any way that is convenient, and it may also be helpful to have some reviewers read through the Profile in its entirety to identify inconsistencies/gaps
- After internal BC review has been completed and the public comment resolutions document has been finalized, an MSK BC vote-to-publish as Stage 2: Consensus will be initiated (goal is to vote by the end of the summer)

Next Call: Tuesday, June 22, 2021 at 10 a.m. CT [4th Tuesday of each month]
