LETTER

REPLY TO ROEMER AND GUERMAZI:

Early biochemical changes on MRI can predict risk of symptomatic progression

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We thank Roemer and Guermazi for their Letter, "Biochemical cartilage changes based on MRI-defined T2 relaxation times do not equal OA detection" (1).

In their comments on our paper (2), the authors (1) raise questions about osteoarthritis (OA) incidence, visual signs of disease on the images, MRI-based scoring systems, and radiomics which we address below.

In ref. 2, we propose a fully automated machine learning technique for discovery of imaging biomarkers in the cartilage of asymptomatic individuals for prediction of future symptomatic OA. We overcome a long-standing limitation of machine learning regarding explainability, by enabling visual recognition of classification biomarkers.

First, regarding OA incidence, the American College of Rheumatology publication (3) cited by the authors (1) recommends diagnosis based on clinical symptoms, radiographs, or laboratory tests, as "no single set of classification criteria could satisfy all circumstances to which the criteria for OA of the knee would be applied. For that reason, the subcommittee elected to design separate sets of classification that might be utilized under different circumstances." Toward this, our study focuses on individuals with minimal radiographic OA and pain at baseline. We used the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score and Kellgren–Lawrence (KL) score to quantify symptoms and radiographic changes, respectively. The definition of KL ≤ 1 as no "definite" radiographic evidence of OA had been used previously (4) in a study of 4,369 participants and in ref. 5, where radiographic OA was KL ≥ 2. In the Osteoarthritis Initiative, radiographic knee OA was defined as KL ≥ 2 (6). The Foundation for the NIH defines knee pain progression as persistent increase in total WOMAC pain score (≥ 9, 0 to 100 scale) from baseline (7). In our study (2), a change in WOMAC of 23.9 ± 10 was found in progressor group vs. -0.4 ± 2.0 in controls in 3 years ($P < 0.001$). Our metrics are aligned with the goals and scope of the paper, which was to detect imaging biomarkers at baseline that could predict symptom progression in the future and are consistent with prior literature.

Second, regarding visual cartilage signs (8), whole-organ magnetic resonance imaging scores were quantified visually, yet only achieved a prediction accuracy of 60% against our fully automated approach.

Third, regarding MRI-based scoring, the paper by Hunter et al. (9) cited by the authors (1) states that the "MRI definition of knee OA . . . requires further formal testing with regards . . . diagnostic performance (especially in . . . persons with early disease), before they are more widely used." The paper by Schiphof et al. (10) cited by the authors compares MRI-based changes to radiographic changes at KL ≥ 2, by which point OA is already clinically apparent by the standard definitions. In contrast, our paper investigates MRI specifically as a modality in the early stages to assess cartilage changes at KL ≤ 1 when symptoms are not yet apparent by clinical definition.

Fourth, we agree that radiomics and feature extraction may help improve prediction of disease incidence and progression of OA, particularly on modalities beyond radiography (11). To this end, the unique contribution of our paper is the ability to quantify discriminating features from cartilage without human input, and their visualization and interpretability.

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The authors declare no competing interest.

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