Purpose: To overcome challenges of the spatial heterogeneity of MRI-based subregional cartilage loss in OA, an ordered value (OV) approach was proposed. This approach ranks subregional cartilage thickness changes in each knee according to magnitude, assigning the region with the greatest cartilage loss to OV1, the one with the 2nd greatest loss to OV2, and the one with the smallest loss or largest increase in thickness to OV16. The approach includes 8 medial and 8 lateral femoral subregions and was shown to be effective in differentiating rates of cartilage loss in OA knees with and without JSN. Here we explore, by simulation, to what extent the OV approach is superior in identifying potential effects of a DMOAD on structural progression in OA.

Methods: 610 knees with radiographic OA (300 with JSN; 310 without) from the Osteoarthritis Initiative were analyzed at baseline and 12 month follow-up (public use data sets 0.E.1, 1.E.1, 0.2.2). The knees were randomized into two equally sized groups. The following simulations were performed: A) all negative subregional changes (thickness loss) were reduced in the treatment group, B) all positive changes (thickening; swelling or hypertrophy) were reduced, C) both types of changes were reduced, assuming a 25% reduction by a DMOAD. For each of the three simulations, the following models were run 1) homogeneous reduction of 25% in each subregion in the treatment group; 2) random reductions between 0% and 50% (mean=25%, SD=12.5%) across knees, but the same value in all subregions of each knee; 3) random reductions between 0% and 50% (mean 25%, SD=12.5%) across different subregions and knees. Effects were reported when consistent results were obtained for simulating the DMOAD effect in each of the randomized subcohorts versus the other (as a placebo [Mann-Whitney-U test: p<0.01]).

Results: Running simulations A-C and models 1-3, significant treatment effects were occasionally observed in cartilage compartments, plates and subregions, but in no case these were consistent when simulating treatment effects in the other randomized subcohort. In contrast, OV1 revealed consistent significant differences in the treated vs. placebo group (p for OV1 between 4.4×10^-7 and 1.1×10^-11), and OV15 displayed significant results in all models, independent of whether the treatment was simulated for one or the other randomized subcohort. This also applied when simulating a DMOAD reducing cartilage thickening, with OV16 displaying treatment-related p-values of 1.5×10^-7 to 7.7×10^-12, and with OV13-16 displaying consistent significance across all models. Simulation of a DMOAD stabilizing cartilage generated p-values for treatment effects between 1.2×10^-5 and 9.2×10^-11 in OV1, and values of 3.3×10^-096 to 4.0×10^-11 in OV16, independent of which randomized subcohort was used.

Conclusion: Limitations of the study are that subregional changes are partly due to precision error, and that it is unknown to what extent DMOADs can reduce (subregional) cartilage thinning or thickening. Therefore, a conservative DMOAD effect of only 25% was applied. A strength of the approach was that the simulation accounted for potential variability of treatment effects between knees and regions, and that the simulation was based on actual measurements of (subregional) cartilage change in OA participants. Therefore, the principal observations should hold, even if the actual magnitude of the effect of a DMOAD was larger or smaller. The results suggest that a) the OV approach is more effective in detecting DMOAD effects than the conventional approach, b) that, unlike conventional approaches, it is capable of capturing effects of a drug stabilizing cartilage (i.e. reducing both loss and thickening), and c) that the OV approach is less sensitive to randomization effects than region based analysis of cartilage loss.

These results will have to be confirmed empirically; the current simulation, however, suggests that ordered values (OVs) of subregional cartilage change in MRI are a potentially very powerful tool for detecting drug effects on structural progression in OA.