Automatic Quantification of Cartilage from MRI for Clinical Studies in OA

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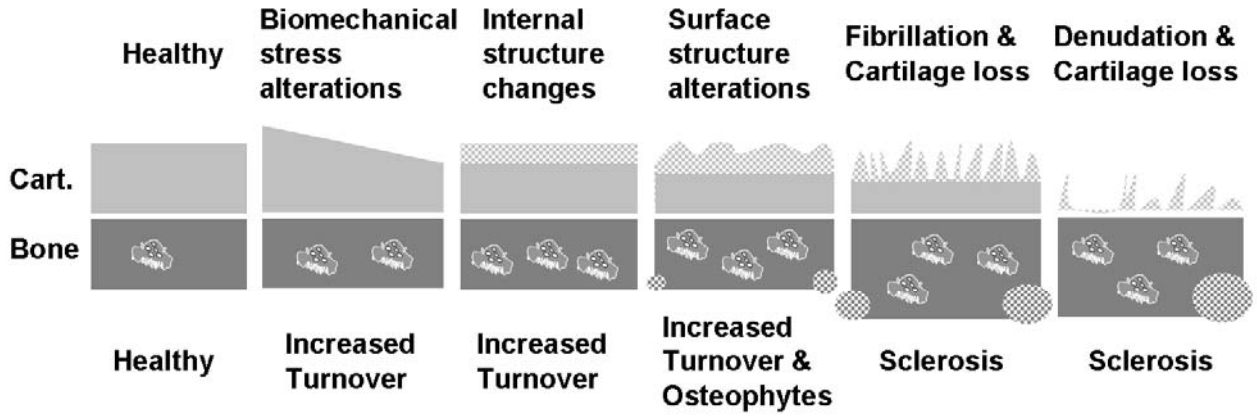
Summary

- Fully automatic, computer-based framework for cartilage quantification
- Independent of scanner, but evaluated for 3D T1 sequence on a 0.18T scanner
- Including markers for all stages of OA
- Including markers for study population selection as well as disease progression

OA Progression: Markers for each Stage

Cartilage degradation and loss occurs gradually during Osteoarthritis (OA). During the very early stages of OA, cartilage quantity is preserved while cartilage quality is affected through increased turnover and early disruption of the extra-cellular matrix. As OA progresses, the cartilage surface integrity is compromised and fibrillation occurs together with focal lesions. The later stages of OA are characterized by larger lesions and more pronounced cartilage loss.



OA Stage:	Pre OA	Very Early	Early	Moderate	Severe
	KL 0	KL 1		KL 2	KL 3 / KL 4
MRI Marker:	Congruity	Homogeneity	Smoothness	Thickness	Volume

These stages of cartilage degradation are illustrated above. The table illustrates that the traditional Kellgren & Lawrence score puts large emphasis on the later stages. This is even more the case for the current gold standard marker for clinical studies – joint space narrowing measured from radiographs.

In our framework for automatic quantification of cartilage from MRI, we have designed markers targeting each of the proposed stages of OA:

- Congruity reveals predisposition for OA by analyzing the large scale cartilage surface curvature.
- Homogeneity quantifies the internal structural integrity by measuring the entropy of the signal intensities in the MRI. This measure of cartilage quality is both a predictor of cartilage loss and by itself a marker for early progression.
- Smoothness quantifies the small scale surface curvature and is linked to fibrillation and the early focal lesions.
- Thickness allows visualization and quantification of thickness maps of the cartilage sheets. This allows analysis of focal cartilage loss.
- Volume is the traditional measure of cartilage loss in each compartment.

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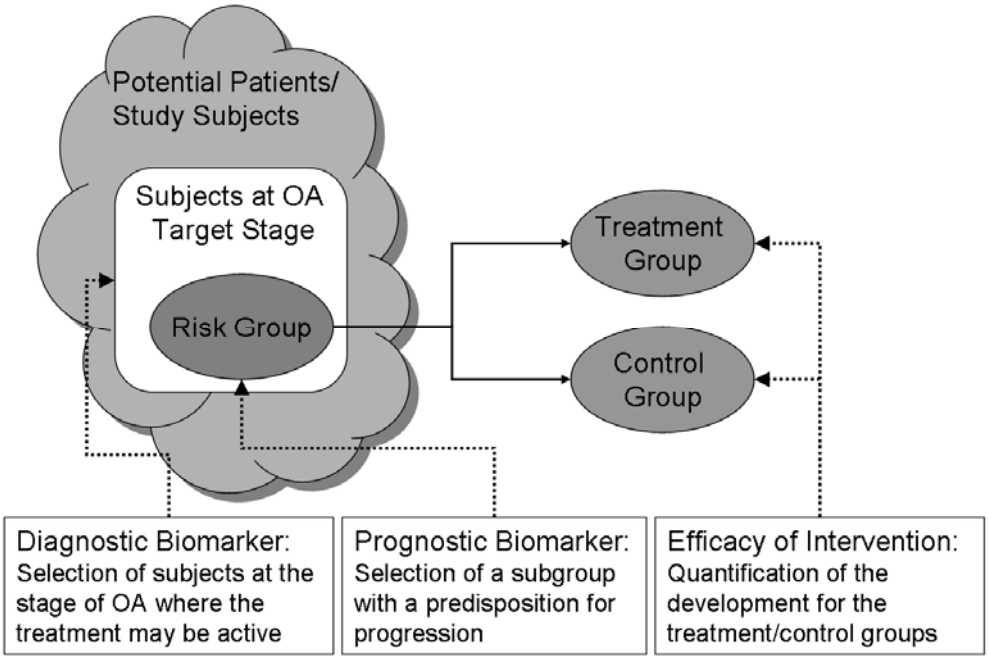
Markers in Clinical Studies: BIPED

Markers should not only be designed for specific stages of OA as outlined above, they also need to solve different tasks in a clinical study. The BIPED categorization emphasizes this as illustrated below.



A diagnostic marker should be used during screening to ensure that the study population is at the stage of OA that the treatment is targeting. Furthermore, in order to ensure progression in the control group, it is essential to select a study population with a high risk of progression. Therefore, a prognostic marker is also needed during screening. Finally, an efficacy marker is needed to quantify the longitudinal changes with a sufficient sensitivity to allow separation of treatment and control and show a treatment effect.

Selected Markers: Volume, Homogeneity, and Longevity

Each of the MRI cartilage markers listed above are appropriate at a specific range of OA stages and for study population selection and/or efficacy quantification. For this small appetizer to the markers developed at Nordic Bioscience Imaging, we have selected three key markers:

Volume	This is the most obvious MRI marker of OA progression and the most likely choice for a new gold standard marker for clinical studies (to replace joint space narrowing measured in radiographs). The marker can be used as efficacy marker from moderate to severe OA. Since FDA is currently focused on late stage OA (symptomatic OA with KL 2-4), cartilage Volume this is currently a natural choice as study endpoint.
Homogeneity	The quantification of structural cartilage integrity measured by our Homogeneity marker can be used both for study population selection and as efficacy marker. Unlike Volume, Homogeneity would be an appropriate efficacy marker for studies evaluating treatments targeting the early stages of OA. For studies focusing on moderate or severe OA, Homogeneity is a good choice for a prognostic marker to be used for study population selection. This will allow selection of subjects where the internal cartilage quality has been compromised – implying an elevated risk of cartilage loss.
Longevity	The Homogeneity marker is a strong prognostic marker. However, in combination with a biochemical marker of cartilage degradation, the ability to predict disease progression becomes even stronger. Where homogeneity reveals weakening of the cartilage, the biochemical marker of degradation of collagen type II, CTX-II, directly quantifies the current degree of breakdown. The combination of the current state – measured by MRI – and the current breakdown, we quantify by the cartilage Longevity marker. This allows superior study population selection.