Detecting subjects at risk of radiological progression: Data from the OAI

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INTRODUCTION: Disease modifying osteoarthritis (OA) drug (DMOAD) trials are hampered by the slow progression of OA. Drug companies address the issue by including patients that are at risk of progression (Early OA, Obesity, malalignment, older age, women, etc.); but current criteria have been proven to be very inefficient at predicting progression.

Purpose:

1) Identify X-Ray quantitative features that are typical of OA subjects who will progress during the next two years.
2) Develop an X-ray based OA progression index that can be used to screen for subjects who are at risk of radiological worsening.
3) Evaluate the standard response of the mean (SMR) of the set composed of subjects identified at risk of OA progression.

Methods:

Quantitative joint space width (qJSW) measurements and semi-quantitative central readings of the knee for Kellgren & Lawrence (KL) grade and radiographic features of the tibio-femoral joint from fixed-flexion knee radiographs from the OAI were used in this study (https://oai.epi-ucsf.org/datarelease/ImageAssessments.asp). The qJSW set is composed of 21 continuous measurements and from those we derived 12 descriptive measurements for a total of 33 quantitative features. We used the qJSW and semi-quantitative assessment of the baseline, 12 month and 24 month x-rays. We also included the 36 and 48 month qJSW data. We complemented the data by including age, gender, weight, height, BMI, site information and the scan date from the clinical and enrollee OAI data sets. Only knees with complete qJSW data and KL scores were included. We used all the longitudinal data to detect and adjust for potential site-specific drift in qJSW. We adjusted qJSW data for height, age and gender correlations using healthy subjects (KL=0) as a normal reference. After adjustment, all measurements were z-transformed. Then, we split the subjects into a training set (1/3 of the population) and test set (the reaming 2/3). From the training set, we selected subjects that had a baseline KL score of 2 or 3. After that, we labeled subjects as progressors or non progressors based on change between the baseline and 24-month exams of OARSI scores of medial and/or lateral joint space narrowing scores. The labeled train-set was explored by B:SWiMS (https://cran.r-project.org/web/packages/FRESA.CAD). B:SWiMS returned a set of compact features that were more common in subjects whose semi-quantitative scores worsened. B:SWiMS also returned a logistic model that can be used to gauge the risk of progression of any OA subject. Finally, we tested the performance of the index on the test set. The performance evaluation included ODDS ratios and SRM metrics.

Results:

5211 knees (3109 females, age 61.8 ± 9.1) had complete qJSW and semi-quantitate KL scores at baseline. At baseline 988, 803, 2118, 1086 and 216 subjects had KL scores of 0, 1, 2, 3 and 4 respectively. The train set consisted of 745 subjects, 207 which had OARSI JSW progression. Figure 1 shows the heat map of features associated with OA progression. B:SWiMS identified that having an abnormal difference between medial and lateral JSW, or a large variance in the medial JSW or abnormal slope between the medial and lateral JSW measurements are baseline characteristics of subjects that will worsen OARSI scores within a 2 year period (Table 1). Those features were incorporated into a logistic model. The model was tested on 1851 knees with either KL=2 (n=1229) or KL=3 (622) and 423 of them had radiological worsening according to the JSN scores. The index showed a test sensitivity of 0.85 with a specificity of 0.45 with a diagnostic odds ratio of 4.6 (95% CI 3.7 to 5.8) Figure 2. The SRM of the OARSI JSN was 0.69 on subjects identified at risk of progression (n=426) and it was superior to the SRM of 0.43 of the entire test set (n=1673)

Conclusions:

There are quantitative X-ray features that are unique in subjects that will progress during the ensuing two years. The logistic model composed by these features enabled the identification of subjects that are at risk of progression with a test sensitivity of 0.85. Screening for subjects with these features may boost the SRM of radiological features by 60%.

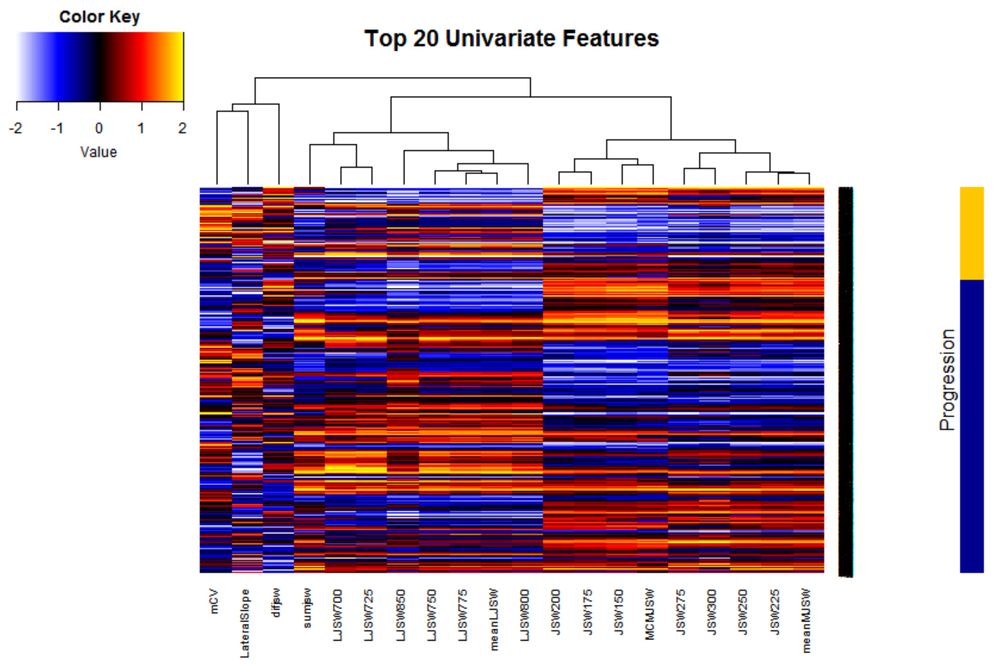

Figure 1: Heat Map of the top 20 features that may be used to predict RX progression

		Train Set (n=745) OR=18.3 (95% CI 11.08 to 30.10)		Test Set (n=1851) OR= 4.6 (95% CI 3.66 to 5.83)			
		No Progressor n=538	2Y Progression n=207	No Progressor n=1428	2Y Progression n=423	Entire Set n=1673	At Risk Set n=426
At Risk Model	Feature	Mean±STD	Mean±STD	Mean±STD	Mean±STD	2Y SRM	2Y SRM
	mCV	0.11±1.07	1.02±1.77	0.42±1.39	1.11±2.12	0.203	0.275
	*Slope	0.30±1.41	0.77±2.58	0.42±1.82	0.69±2.71	0.055	0.108
	stdMJSW	0.00±0.95	0.16±1.03	0.10±1.04	0.18±1.25	-0.062	-0.143
	*Diff	-0.27±1.38	-0.68±2.47	-0.37±1.75	-0.60±2.58	-0.046	-0.101
JSN Scores	med JSN	0.56±0.50	1.16±0.88	0.83±0.76	1.14±0.88	0.354	0.556
	lat JSN	0.10±0.30	0.34±0.67	0.16±0.48	0.41±0.73	0.223	0.325
	mJSN+lJSN	0.66±0.50	1.50±0.67	1.00±0.77	1.56±0.68	0.429	0.694

Table 1: The features of the progression Index on the train at test sets are shown in the top four rows. The last three rows shows the behavior of the JSN OARSI scores on the same train and test sets. The last column is the set of subjects that were identified at risk of progression. The subjects at risk showed a SRM of **0.694** compared to the 0.429 of the test cohort.

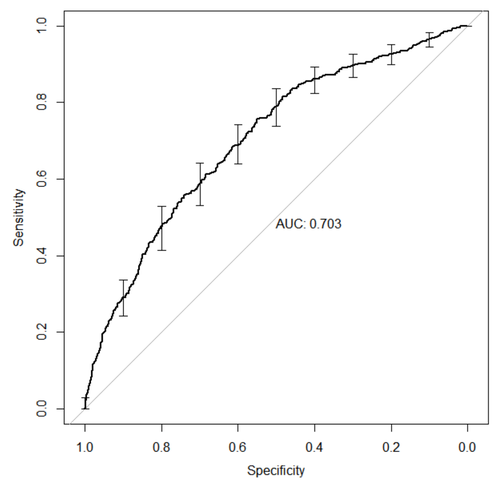

Figure 2: ROC analysis of the RX progression index on the test data set.

Acknowledgment:

• Funded in part by NIAMS (contracts N01-AR-2-2261, N01-AR-2-2262 and N01-AR-2-2258).