

1 The Role of Magnetic Resonance Imaging in Classifying Individuals Who Will Develop
2 Accelerated Knee Osteoarthritis

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40 analysis and interpretation of data. Duryea, MacKay, Pang, and Davis contributed to both
41 acquisition of data and interpretation of data.

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45

46 **ABSTRACT**

47 We assessed whether adding magnetic resonance (MR)-based features to a base model of
48 clinically accessible risk factors (i.e., serological, radiographic, demographic, symptoms, and
49 physical function) improved classification of adults who developed accelerated knee
50 osteoarthritis (KOA) or not over the subsequent 4 years. We conducted a case-control study
51 using radiographs from baseline and the first four annual visits of the Osteoarthritis Initiative to
52 define groups. Eligible individuals had no radiographic KOA in either knee at baseline
53 (Kellgren-Lawrence grade (KL) <2). We classified 2 groups matched on sex: 1) accelerated
54 KOA: at least one knee developed advanced-stage KOA (KL=3 or 4) within 48 months and 2)
55 did not develop accelerated KOA within 48 months. The MR-based features were assessments of
56 bone, effusion/synovitis, tendons, ligaments, cartilage, and meniscus. All risk factors and MR-
57 based features were from the baseline visit. Classification and regression tree analyses were
58 performed to determine classification rules and identify important variables. The base CART
59 model and the base model + MR features each explained approximately 40% of the variability.
60 Adding MR-based features to the base model yielded modest improvements in specificity (0.90
61 versus 0.82) but lower sensitivity (0.62 versus and 0.70) than the base model. There was
62 consistent evidence that serum glucose, effusion-synovitis volume, and cruciate ligament
63 degeneration are important variables in classifying individuals who will develop accelerated
64 KOA. We found common MR-based measures failed to dramatically improve classification.
65 These findings also show a complex interplay among risk factors and a need to identify novel
66 risk factors to improve classification.

67

68

69 **INTRODUCTION**

70 Knee osteoarthritis (KOA) is typically considered a slowly progressive disorder.
71 However, at least 1 in 5 cases of incident KOA develop an accelerated form of KOA,
72 progressing from no radiographic KOA to advanced-stage KOA within 4 years and often within
73 12 months.¹⁻³ Adults with accelerated KOA experience greater pain and functional disability than
74 those with a typical onset of KOA.^{2; 4} Since the rate of disease onset offers only a short
75 opportunity to intervene it would be helpful to classify people at-risk for accelerated KOA to
76 create an opportunity to develop and deliver prevention strategies. We previously classified
77 individuals using serum, radiographic, and demographic/anthropometric (age and body mass
78 index) risk factors and explained 31% of the variability with high specificity but low sensitivity.⁵
79 These results suggest that further analyses are needed with additional outcomes to better
80 discriminate between individuals that will and will not develop accelerated KOA.

81 Prodromal symptoms, functional disability, and magnetic resonance (MR) imaging-based
82 knee assessments may help classify adults at risk for accelerated KOA. Adults who develop
83 accelerated KOA often report greater prodromal symptoms and experience greater functional
84 disability (e.g., slower walking speed) than those with typical KOA up to 3 years prior to
85 radiographic onset.² More recently, magnetic resonance (MR)-based measurements have also
86 been identified as risk factors or early signs of accelerated KOA (e.g., effusion-synovitis,
87 meniscal pathology).⁶⁻⁹

88 The purpose of this study was to utilize classification and regression tree (CART) models
89 to 1) assess the ability of MR features from the baseline visit to classify participants who will
90 and will not develop accelerated KOA in the subsequent 4 years, and 2) determine whether
91 adding baseline MR features to a base model that incorporated measures of symptoms, function,

92 radiographic, clinical, and demographic characteristics from the baseline visit improves
93 classification of adults who will develop accelerated KOA over the subsequent 4 years.

94

95 **METHODS**

96 We conducted a case-control study using data and images from baseline and the first 4
97 annual visits in the Osteoarthritis Initiative (OAI), a longitudinal multicenter observational
98 cohort study of adults with or at risk of developing symptomatic KOA. Almost 4,800 participants
99 (ages 45-79 years) were enrolled at 4 clinical sites in the United States between February 2004
100 and May 2006.¹⁰ The protocol and detailed descriptions of the eligibility criteria are available at
101 the OAI website.¹⁰ Institutional review boards at each of the 4 clinical sites and the OAI
102 coordinating center approved the study. All participants provided informed consent.

103

104 **Case and Control Definitions**

105 Group assignment (accelerated KOA, typical KOA, and no KOA) was determined using
106 annual radiographs from the baseline to the 48-month OAI visits. Eligible participants had
107 Kellgren-Lawrence (KL) grade < 2 at baseline in both knees. Cases were participants with
108 accelerated KOA, defined as the development of advanced-stage KOA (KL grade 3 or 4) by the
109 48-month visit. Typical KOA was defined as an increase in radiographic severity (KL grade) by
110 month 48 (excluding those meeting the definition for accelerated KOA). No KOA was defined as
111 no increase in the KL grade by month 48. Adults with typical KOA and no KOA were controls.

112 We matched typical KOA and no KOA participants by sex to the accelerated KOA group
113 (cases, n=54) in a 1:1:1 matching scheme. For the purposes of this study, typical KOA and no
114 KOA participants were combined into one group to explore whether risk factors or combinations

115 of risk factors were able to classify adults who would develop accelerated KOA. The knee that
116 first met the criteria for accelerated or typical KOA was included in the analysis. Participants
117 with no KOA were side-matched to the accelerated KOA knee.

118 To determine eligibility and group assignment we relied on bilateral weight-bearing,
119 fixed-flexion posteroanterior knee radiographs. Central readers scored the KL grade of each knee
120 (KL0 to KL4), with KL4 indicating the worst radiographic KOA severity. Good intra-rater
121 reliability was observed for KL grade (weighted $\kappa = 0.70$ to 0.78).¹⁰ The protocol and data are
122 publicly available at the OAI website (Files: kXR_SQ_BU##_SAS; versions 0.6, 1.6, 3.5, 5.5,
123 6.3).¹⁰

124

125 **Candidate Measures from the Base CART Model**

126 Measures from the baseline visit that were clinically-accessible were chosen as candidate
127 variables: radiographic assessments, demographic characteristics (age, sex, and body mass
128 index), biospecimen measurements, symptoms (pain, function, quality of life, swelling and
129 tenderness), and walking speed. These are described more fully in the following sections and in

130 **Supplement Table 1.**

131

132 ***Radiographic Assessments***

133 We used bilateral weight-bearing, fixed-flexion posteroanterior knee radiographs to
134 assess two radiographic variables: femorotibial angle (FTA) and coronal tibial slope.

135 Femorotibial angle was measured to assess static knee alignment. We used the publicly
136 available data on the OAI website (file: KXR_FTA_Duryea00, version 0.2).¹⁰ In brief, a
137 customized software tool defined the tibial axis based on the central point of the knee and the

138 center of the tibial diaphysis at approximately 10 cm distal to the tibial plateau. The femoral axis
139 was perpendicular to a line tangent to the distal ends of the medial and lateral femoral condyles.
140 The software tool calculated the angle between the tibial and femoral axis with negative values
141 indicating knees with more varus alignment. FTA was adjusted to match hip-knee-ankle angles
142 as described in Iranpour-Boroujeni et al.¹¹ Intra-reader and inter-reader ICCs were >0.95.¹⁰

143 Coronal tibial slope was assessed by one reader (JBD) using an EFilm Workstation 3.4
144 (Merge Healthcare, Chicago, IL).¹² The reader identified the longitudinal tibial axis and drew a
145 line connecting the peak points of the medial and lateral aspects of the tibial plateau. He then
146 moved the longitudinal axis to the lateral aspect of the tibial plateau and drew a line
147 perpendicular to the longitudinal axis. A positive coronal tibial slope indicated that the peak
148 lateral aspect of the tibial plateau was proximal to the peak medial aspect. The intra-reader
149 reliability was good (ICC_{3,1}=0.87, n=15 knees).¹³

150

151 *Demographic Characteristics*

152 We included publicly available age, sex, and body mass index, which study staff
153 collected at baseline per a standard protocol (Files: enrollees, version 22; allclinical00, version
154 02.2.).¹⁰

155

156 *Biospecimens*

157 Study staff performed blood draws at the baseline visit. Participants fasted for at least 8
158 hours prior to the blood draw. Blood samples were centrifuged and aliquoted into cryovials.
159 Samples were stored in a -70°C freezer prior to shipping to Fisher Bioservices (Rockville, MD)
160 for long-term storage. Protocols for the biospecimens collection and processing are available on

161 the OAI website.¹⁰ Fisher Bioservices shipped the serum samples to Temple University School
162 of Medicine in September 2015. One investigator (MA) performed all assays in duplicate. We
163 used commercially available enzyme-linked immunosorbent assay kits to assess high-sensitivity
164 C-reactive protein (Novex by Life Technology, Carlsbad, CA) and glycated serum protein
165 (MyBiosource, San Diego, CA). The Abcam Glucose Assay Kits were used to assess serum
166 glucose (after deproteinization). Further details about the biospecimen analysis for this study
167 were previously described.¹⁴

168

169 *Symptoms*

170 In addition to the measures in the previously published CART model (described above),⁵
171 we included clinically accessible pain, function, clinical knee exam, and quality of life measures
172 in our base model. All data are publicly available (File: allclinical00, version 0.2.2).¹⁰

173 The Western Ontario and McMaster (WOMAC) Universities Osteoarthritis Pain Scale
174 (3.1 Likert version) was used to assess self-reported knee-specific pain within the last 7 days
175 separately for each knee (range 0-20, with higher scores indicating higher pain).¹⁵ The scale is
176 based on 5 questions about pain, each scored from 0 (no pain) to 4 (extreme pain). (The
177 WOMAC Function Scale (3.1 Likert version) function scores range from 0-68, with higher
178 scores indicating greater functional impairment. The scale is based on 17 questions, each scored
179 from 0 (no impairment) to 4 (extreme impairment).

180 Separately, participants were asked whether “during the past twelve months, have you
181 had pain, aching or stiffness, in or around your right knee, on most days for at least one month?
182 By most days, we mean more than half the days in one month.” Possible responses were yes or
183 no. A similar question was asked about the left knee.

184 Participants also self-reported impact of KOA on quality of life via the Knee Injury and
185 Osteoarthritis Outcome Score (KOOS) quality of life subscale.¹⁶ Possible scores range from 0-
186 100, with higher scores indicating better quality of life.

187 Bilateral clinical knee exams were performed at baseline to determine the presence of
188 crepitus, tenderness and/or swelling. Specifically, we included patella-femoral crepitus, lateral
189 and medial joint line tenderness, patella tenderness, knee swelling evidenced by a positive bulge
190 sign or patellar tap test, and patellar/quadriceps tenderness/tendonitis.

191

192 ***Physical Function***

193 Habitual walking speed was assessed via 2 timed 20-meter walks. The time needed to
194 complete the 20-meters was converted to walking speed (i.e. meters/second [m/s]) and averaged
195 across the two trials. All data are publicly available (File: allclinical00, version 0.2.2).¹⁰

196

197 **MR-based Features Added to the CART**

198 ***Magnetic Resonance Imaging Acquisition***

199 Baseline MR images were acquired with one of four identical Siemens (Erlangen,
200 Germany) Trio 3-Tesla MR systems at each clinical site using the OAI MR imaging protocol.¹⁰
201 ¹⁷ Bone marrow lesion (BML) volume and effusion-synovitis volume quantitative measurements
202 were performed using a sagittal intermediate-weighted, turbo spin echo, fat-suppressed MR
203 sequence with the following parameters: field of view=160mm, slice thickness=3mm,
204 skip=0mm, flip angle=180 degrees, echo time=30ms, recovery time=3200ms, 313x448 matrix, x
205 resolution=0.357mm, y resolution=0.511mm, and total slice number=37. Articular cartilage was
206 quantified using a 3-dimensional dual-echo steady-state sequence with the following parameters:

207 field of view=140mm, slice thickness=0.7mm, skip=0mm, flip angle=25 degrees, echo
208 time=4.7ms, recovery time=16.3ms, 307x384 matrix, x resolution=0.365mm, y
209 resolution=0.456mm, and total slice number=160. Musculoskeletal radiologists assessed semi-
210 quantitative or dichotomous MR-based features using all MR sequences for each visit.

211

212 ***Bone Marrow Lesion Volume***

213 One reader (ACS), unaware of group assignment, measured tibiofemoral BML volume
214 with a semi-automated segmentation software.^{18, 19} The only manual step required the reader to
215 identify crude boundaries of the tibia and femur in each slice of the MR sequence. The boundary
216 furthest from the articular surfaces was marked just prior to the epiphyseal line or at the edge of
217 the bone and soft tissue. The program then automatically identified the precise bone boundaries
218 and performed a thresholding and curve evolution process twice to segment areas of high signal
219 intensity, which may represent a BML. We eliminated false-positive regions by operationally
220 defining a BML based on 2 criteria: 1) the distance between a BML to the articular surface
221 should be <10 mm, and 2) a BML needed to span more than one MR image. The study principal
222 investigator reviewed all measurements. Our reader demonstrated excellent intra-reader
223 reliability (ICC_{3,1}=0.91). Total tibiofemoral BML volume was used in the analysis.

224

225 ***Effusion-Synovitis Volume***

226 We used a semi-automated segmentation software to measure knee effusion-synovitis,
227 which reflects effusion and synovitis volume.⁶ Two readers (JBD and FA) used the software to
228 mark the first and last MR slice that included bone, the proximal border of the patella, and the
229 apex of the fibular head. The software then automatically segmented effusion-synovitis between

230 these limits based on an existing threshold. The senior reader (JBD) then manually adjusted the
231 threshold to change the effusion-synovitis boundaries and removed areas of high-signal intensity
232 that were not effusion-synovitis (e.g., subchondral cysts, blood vessels). The senior reader
233 demonstrated excellent intra-reader reliability ($ICC_{3,1}=0.96$). Whole knee effusion-synovitis
234 volume was used in the analysis.

235

236 *Cartilage Damage Index*

237 To measure tibiofemoral cartilage we used the validated cartilage damage index (CDI).^{20;}
238 ²¹ One reader (JED) manually marked the bone-cartilage boundary on specific knee slices that
239 are automatically selected based on the presence of predefined informative locations.^{20; 21} The
240 reader then measured cartilage thickness at predefined 36 informative locations, which the
241 software automatically located. The software then computed the CDI for the medial femur,
242 lateral femur, medial tibia, and lateral tibia by summing the products of cartilage thickness,
243 cartilage length (anterior-posterior), and voxel size from 9 informative locations in each region.
244 The study principal investigator reviewed all measurements. Our reader demonstrated excellent
245 intra-reader reliability ($ICC_{3,1}=0.86$ to 0.99). CDI in the medial and lateral compartments of the
246 tibial and femoral were used in the analysis.

247

248 *Semi-quantitative Features*

249 Two musculoskeletal radiologists (RW:255 cases, JM:120 cases) performed the semi-
250 quantitative MR readings. Readers had good agreement on the presence of each pathology
251 among 25 cases: prevalence-adjusted and bias-adjusted kappa were 0.41 to 0.75 except for the

252 posterior horn of the medial meniscus where the prevalence-adjusted and bias-adjusted kappa
253 was fair at 0.25 (50% agreement).

254 The radiologists assessed the integrity of anterior/posterior cruciate ligaments,
255 medial/lateral collateral ligaments, extensor mechanism, and gastrocnemius proximal tendons by
256 noting if the structures appeared normal or degenerative. Degenerative tissue was defined as the
257 presence of abnormal intrinsic high-signal intensity within the substance of the ligaments or
258 tendon without discrete tear. Degenerative cruciate ligament pathology combined the presence of
259 anterior or posterior cruciate ligament degenerative pathology. Degenerative collateral ligament
260 pathology combined the presence of medial or lateral collateral ligament degenerative pathology.

261 The radiologists scored infrapatellar fat pad signal intensity alteration using the MR
262 Imaging Osteoarthritis Knee Score grading system (i.e., normal, mild, moderate, and severe).²²
263 Infrapatellar fat pad signal intensity was recoded as absence (i.e., normal) or presence (i.e., mild,
264 moderate, and severe).

265 The radiologists scored medial and lateral meniscus extrusion using the MR Imaging
266 Osteoarthritis Knee Score grading system (i.e., Grade 0: <2 mm, Grade 1: 2 to 2.9 mm, Grade 2:
267 3 to 5 mm, and Grade 3: >5mm).²² Meniscal extrusion was recoded as absence (i.e., Grade 0) or
268 presence (i.e., \geq Grade 1).

269 The radiologists used the International Society of Arthroscopy, Knee Surgery, and
270 Orthopaedic Sports Medicine meniscal tear classification, which was modified for MR
271 imaging²³, to assess the body, posterior/anterior horn of each meniscus as: normal, degeneration,
272 horizontal, flap horizontal, vertical longitudinal, radial, morphologic deformity, maceration,
273 complex, or vertical flap tear. Meniscal pathology was recoded as absence (i.e., normal or
274 degeneration without tear) and presence (i.e., horizontal, flap horizontal, vertical longitudinal,

275 radial, morphologic deformity, maceration, complex, or vertical flap tear). The medial/lateral
276 menisci were considered pathologic if pathology was present in any of the three regions (body or
277 anterior/posterior horn). Additionally, we determined the number of pathologic meniscal regions
278 with meniscal pathology, which could range from 0-6 (i.e., medial/lateral and
279 anterior/body/posterior horn).

280 The radiologists were also asked to record the presence of any other miscellaneous
281 pathology: attrition, acute ligamentous or tendinous injuries, subchondral insufficiency fractures,
282 and any other incidental findings. Attrition was assessed from 0 (normal) to 3 (severe), based on
283 the perceived degree of deviation from a normal contour for the medial and lateral femur and
284 tibia. We defined the presence of attrition as a score of 1 or more. We defined acute ligamentous
285 or tendinous injury as per routine clinical practice, using the presence/absence of focal fiber
286 disruption and intrinsic ligamentous or subjacent soft tissue edema to detect the presence of
287 injury. We defined subchondral insufficiency fracture as a linear low signal in the subchondral
288 bone on a fat suppressed image and subjacent edema. Since each of these pathologies were rare,
289 we combined them into a single outcome variable: presence or absence of miscellaneous
290 pathology.

291

292 **Statistical Analysis**

293 We performed classification and regression tree (CART) analyses to determine
294 classification rules and important variables for: 1) a model with MR variables only, 2) a base
295 model with clinically accessible variables (i.e., serological, radiographic, demographic,
296 symptoms, and physical function), and 3) a combined model with all clinically accessible
297 variables and MR-based measures as candidate variables.

298 CART is a non-parametric method that has some advantages over other statistical
299 techniques for classification by allowing for complex interactions and non-linear associations.
300 This method identifies the most discriminating risk factor, with its associated cut point, to
301 differentiate the two groups (e.g. accelerated KOA or no accelerated KOA). After the initial split
302 based on the cut point, CART iteratively finds the next best risk factors with their corresponding
303 associated cut point. CART analysis identifies the most important risk factors and is easily
304 interpretable. The identification of important variables is obtained by creating multiple trees via
305 cross-validation, and observing which variables appear in most of the trees.²⁴

306 Pruning and 10-fold cross-validation were performed to avoid overfitting and to identify
307 the most important variables. Sensitivity and specificity were calculated for all models. All
308 analyses were performed using the rpart function in R (version 3.4.4, The R Foundation for
309 Statistical Computing).

310

311 **RESULTS**

312 Fifty-four cases (accelerated KOA) and 108 participants in the control group (54 adults
313 with typical KOA and 54 adults with no KOA) met the inclusion criteria at baseline. This cohort
314 has been described previously.⁵ In brief, the sample was predominantly female (63%), with mean
315 age 59 years (SD=8), and body mass index 28 kg/m² (SD=5).

316

317 *Model 1: CART with MR Features Only*

318 **Figure 1** displays the CART model with only MR features to see which features are
319 associated with development of accelerated KOA. Effusion-synovitis volume, BML volume, and
320 presence of cruciate ligament degeneration were the three most important variables (in order of

321 importance). Individuals with a higher effusion-synovitis volume (≥ 14 cc) were likely to develop
322 accelerated KOA over the subsequent 4 years. Participants with a lower effusion-synovitis
323 volume but larger BML volume (> 0.24 cc) were less likely to develop accelerated KOA. In
324 contrast, adults with lower effusion-synovitis and BML volumes and cruciate ligament
325 degeneration were more likely to develop accelerated KOA. This model explained 31% of the
326 variability, with specificity of 0.88 and sensitivity of 0.57.

327

328

329 ***Model 2: Base Model - Previously Published Model + Symptoms and Function***

330 **Figure 2** presents the base model based on clinically accessible variables.⁷ Baseline
331 serum glucose, age, and static alignment were the three most important variables (in order of
332 importance). The first 3 cuts were based on age, serum glucose, and BMI. Most individuals < 64
333 years did not develop accelerated KOA over the subsequent 4 years, except for those with body
334 mass index ≥ 34 kg/m² and those with body mass index < 34 kg/m² but more impaired WOMAC
335 function (≥ 8.8) and coronal tibia slope ≥ 4 degrees (a more proximal lateral plateau than medial).
336 Conversely, all of the adults 64 or older with glucose < 82 developed accelerated KOA. This
337 model explained 41% of the variability and had specificity of 0.82 and sensitivity of 0.70.

338

339 ***Model 3: Base Model + MR Features***

340 **Figure 3** displays the CART with all candidate variables placed in the model. Effusion-
341 synovitis volume, serum glucose, and the presence of cruciate ligament degeneration were the
342 most important variables (in order of importance). Overweight or obese individuals with higher
343 effusion-synovitis volume (≥ 14 cc) were more likely to develop accelerated KOA over the

344 subsequent 4 years. Participants with lower effusion-synovitis volume (<14 cc) and glucose <67
345 were also likely to develop accelerated KOA. The presence of cruciate ligament degeneration
346 and coronal tibial slope played a role in classification of individuals with lower effusion-
347 synovitis volume and glucose \geq 67. This model explained 39% of the variance and had specificity
348 of 0.90 and sensitivity of 0.62.

349

350 **DISCUSSION**

351 We expanded on prior work to classify adults at risk for accelerated KOA by adding
352 baseline clinical, symptomatic, and MR measures to a CART. Our primary goal was to assess
353 whether adding MR measures in isolation or combined to our base model could improve the
354 classification of individuals at risk for developing accelerated KOA within the subsequent four
355 years. Variables that consistently appeared in the models, and that may enable classification of
356 individuals at risk of developing accelerated KOA, were effusion-synovitis volume, presence of
357 cruciate ligament degeneration, and serum glucose. The addition of an array of MR variables to
358 the base model failed to improve model fit (percent of variance explained ~40% for both
359 models).

360 Based our prior analyses^{2, 4}, we hypothesized that the addition of baseline pain, function
361 and quality of life measures would improve the classification of adults who will develop
362 accelerated KOA in the subsequent 4 years. While the model with these measures showed some
363 improvement in terms of the percent of variability explained (41% vs 31% in previously
364 published models), WOMAC function was the only symptom, function, or quality of life variable
365 that was selected by the model. We also hypothesized that the addition of MR measures would
366 improve classification of adults who will develop AKOA, based on prior analyses.^{2, 6-9} However,

367 the base model + MR features explained slightly less variability than the base model alone (39%
368 vs 41%). The full model also had lower sensitivity (0.62 vs 0.70) but higher specificity (0.90 vs
369 0.82) compared to the base model.

370 This lack of substantial improvement in classification after adding variables such as pain
371 that have been shown to be associated with development of accelerated knee osteoarthritis may
372 be explained by the fact that CART's strength is in classification rather than prediction or
373 strength of association. There may be other variables that are more relevant in classification than
374 pain. Additionally, the interactions may identify subsets of people that are more at risk based on
375 their combined characteristics, rather than pain alone.

376 In spite of the improvements in the percent of variability explained by the models with
377 symptoms and MR, 60% of the variance remains unexplained. The cost of obtaining self-
378 reported function, pain, and quality of life is minimal and clinicians and researchers may
379 consider including them when assessing risk for development of accelerated KOA. MR
380 measurement costs, on the other hand, can be quite substantial. It is not clear that there is a
381 sufficient increase in precision of the classification to warrant the additional cost. Identification
382 of novel risk factors may improve classification.

383 Both effusion-synovitis volume and cruciate ligament degeneration are consistently
384 identified as important MR-based features for the classification of accelerated KOA. This
385 complements prior work where we observed effusion-synovitis volume was greater among adults
386 who developed accelerated KOA up to 2 years prior to radiographic onset compared with adults
387 with typical or no KOA.⁶ Furthermore, these results agree with preliminary results that cruciate
388 ligament degeneration is more common among adults who developed accelerated KOA up to 2
389 years prior to radiographic onset compared with adults with typical or no KOA.²⁵ These MR-

390 based findings may be some of the earliest manifestations of accelerated KOA, which could help
391 shed light on why some adults develop accelerated KOA.

392 Despite previous findings that fasting serum glucose was not significantly associated with
393 either prevalent or incident KOA²⁶⁻²⁹, we identified fasting serum glucose as a potentially
394 important variable for classifying people who will develop accelerated KOA. While this finding
395 is surprising, it may be explained by CART's ability to detect possible interactions with small
396 sample sizes, whereas standard statistical analyses would not be powered to detect interactions.
397 For example, the CART results suggest that glucose may be an important factor among older
398 adults, but not among younger adults. It may be useful to explore the association between fasting
399 glucose levels and development of accelerated KOA among adults 64 years and older.

400 CART is useful as an exploratory method to help identify possible risk factors and
401 interactions that are not possible with regression in studies with limited sample size. The CART
402 results suggest that there may be interactions between age, BMI, and glucose in the base model.
403 There may also be interactions between effusion-synovitis volume and BMI, as well as effusion-
404 synovitis volume and glucose. Future studies sufficiently powered to detect interactions will be
405 important in improving classification of people at risk of developing accelerated KOA.

406 While this study has identified potential new risk factors and possible interactions, we
407 acknowledge that there are limitations. We have not yet replicated this model in an external
408 dataset. Although external validation is a critical future project, we are still in the development
409 stage of model development. Our best model still has a significant amount of unexplained
410 variation and we feel this needs to be addressed by identification and inclusion of novel risk
411 factors before proceeding to a standard development and validation model. Despite this

412 limitation, we believe this study is an important step towards classifying adults who will develop
413 accelerated KOA.

414 In conclusion, acquisition of MR images for common structural features to identify individuals at
415 risk of developing accelerated KOA in the subsequent four years may not be justified due to the
416 high cost of obtaining them and the minimal effect on classification compared to the base model.

417 We also found that serum glucose, effusion-synovitis volume, and cruciate ligament
418 degeneration are important variables in the classification of individuals at risk for accelerated
419 KOA in the next four years. However, all models continue to have ~60% of the variability
420 unexplained, indicating a need for future research to identify novel risk factors that will improve
421 the classification.

422

423

424

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533

534 **FIGURE LEGENDS**

535 **Figure 1: Classification and Regression Tree with Features on Magnetic Resonance Images**
536 **Only**

537 Abbreviations: Effusion=effusion-synovitis, BML=bone marrow lesion, AKOA=accelerated
538 knee osteoarthritis

539

540 **Figure 2: Classification and Regression Tree Base Model: Previously Published Model with**
541 **Symptoms and Function Added**

542 Abbreviations: BMI=body mass index, AKOA=accelerated knee osteoarthritis

543

544 **Figure 3: Classification and Regression Tree Base Model and Features on Magnetic**
545 **Resonance Images**

546 Abbreviations: Effusion=effusion-synovitis, BMI=body mass index, AKOA=accelerated knee
547 osteoarthritis

548

549