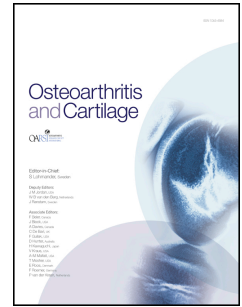


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Significant morphological change in osteoarthritic hips identified over 6-12 months using Statistical Shape Modelling

Rebecca J. Barr, Jennifer S. Gregory, Kanako Yoshida, Salvatore Alesci, Richard M. Aspden, David M. Reid



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1 **Significant morphological change in osteoarthritic hips identified**
2 **over 6-12 months using Statistical Shape Modelling.**

3
4 Rebecca J Barr^{1,2†}, Jennifer S Gregory^{1†}, Kanako Yoshida¹, Salvatore Alesci³, Richard M
5 Aspden¹, David M Reid¹

6 † both authors contributed equally to this paper

7 ¹School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, UK,

8 Current affiliations: ²Medicines Monitoring Unit (MEMO), Division of Molecular & Clinical
9 Medicine, School of Medicine, University of Dundee; ³Takeda Pharmaceuticals, Washington
10 District of Columbia, USA.

11 Rebecca J Barr, r.y.barr@dundee.ac.uk

12 Jennifer S Gregory, j.gregory@abdn.ac.uk

13 Kanako Yoshida, kanako.yoshida@nhs.net

14 Salvatore Alesci, alescis@gmail.com

15 Richard M Aspden, r.aspden@abdn.ac.uk

16 David M Reid, d.m.reid@abdn.ac.uk

17
18 **Corresponding Author**

19 Professor R.M. Aspden
20 Institute of Medical Sciences
21 University of Aberdeen
22 Foresterhill
23 Aberdeen
24 AB25 2ZD
25 r.aspden@abdn.ac.uk
26 +44 1224 437445

27
28 Running title: **Shape changes in hip OA over 12 months**

29

30 **Abstract**

31 **Objective** Predicting who will develop osteoarthritis, assessing how rapidly their disease will
32 progress and monitoring early responses to treatment are key to the development of
33 therapeutic agents able to treat this crippling disease and to their future clinical use.
34 Statistical Shape Modelling (SSM) enables quantification of variations in multiple geometric
35 measures describing the whole hip joint to be considered in concert. This prospective study
36 evaluates the responsiveness of SSM to changes in hip-shape within one year.

37 **Methods** Sixty-two people, mean age 67.1 yrs, were recruited. Dual-energy X-ray
38 Absorptiometry images were taken at three timepoints (baseline, six and twelve months).
39 Based on Kellgren-Lawrence grading (KLG) of their baseline images, subjects were classified
40 into control/doubtful OA: $KLG < 1$ in both hips; moderate OA: $KLG = 2$; and severe OA: $KLG \geq 3$
41 in their most severe hip. Morphology was quantified using SSM and changes in shape were
42 assessed using generalised estimating equations. Standardized response means (SRM) were
43 calculated for the first and second 6 month periods, then the full 12 months.

44 **Results** Disease severity ranged from KLG0-KLG4 in the 124 hips assessed at baseline. Three
45 SSM modes (Modes 1, 3 and 4) were associated with OA severity. Across the whole cohort,
46 SRM magnitudes ranged from 0.16 to 0.63. The greatest subgroup SRM (magnitude 0.91)
47 was observed over 12 months in those subjects with moderate OA (KLG2).

48 **Conclusions** We have demonstrated that SSM can capture changes in hip shape over 6 and
49 12 months across the entire hip joint providing a sensitive measure of hip OA progression.

50

51 **Keywords:** osteoarthritis; statistical shape modelling; morphology; hip; radiographic; DXA

52

1 Introduction

2 Despite the high prevalence of osteoarthritis (OA) there is a dearth of treatments that can
3 modify disease progression, leaving patients with symptomatic relief alone until a joint
4 replacement becomes their only option. Among the reasons for the lack of Disease
5 Modifying Osteoarthritis Drugs (DMOADs) are our current inability to predict who will
6 develop OA, assess how rapidly their disease will progress and monitor treatment success.

7

8 The diagnosis of radiographic OA is made using semi-quantitative scoring systems such as
9 Kellgren-Lawrence grades (KLG), Croft or ACR [1-3]. These scoring systems assign a score to
10 each joint based on a number of primary radiographic features of joint disease including:
11 deformation of the femoral head, osteophytes, subchondral cysts, subchondral sclerosis and
12 reduced joint space width. Although these scoring systems are adequate for radiographic
13 disease diagnosis and broad stratification into control/doubtful, moderate and severe OA
14 they are not sensitive enough to provide a useful tool for the identification of subjects likely
15 to progress rapidly nor for treatment monitoring in clinical trials.

16

17 Joint space width (JSW), a surrogate marker of cartilage loss, is a quantitative measure of OA
18 progression and is currently the only Federal Drugs Administration-approved measure of OA
19 progression. JSW is used as an endpoint in clinical trials of all new DMOADs. However, joint
20 space narrowing focuses on a single feature in a single tissue in a multi-tissue, multi-feature
21 disease.

22

23 In recent years, magnetic resonance imaging has become the mainstay of much of the
24 ongoing OA research on disease progression. There is no doubt that data gained from MR
25 images are invaluable in providing detailed information on bone marrow lesions, cysts and
26 cartilage erosion. However, MR imaging is not suitable for all hip OA patients; not only is it
27 costly but many patients are simply too obese to fit in a standard MR scanner.

28

29 Dual energy X-ray Absorptiometry (DXA) is an imaging modality used in the diagnosis of
30 osteoporosis. In addition to bone mineral density (BMD) data, modern high-resolution
31 scanners, such as the GELunar iDXA, generate near radiographic quality images. These
32 images are currently under-utilised, simply being used to check positioning when capturing
33 BMD data. We have previously demonstrated that these images can be used to grade
34 radiographic OA severity as repeatably as from radiographs [4].

35

36 Statistical shape modelling (SSM) uses Principal Component Analysis to describe variation in
37 the complicated shapes of natural objects [5]. SSMs have previously been applied to images
38 captured by different imaging modalities taken from a number of different sites within the
39 human body including heart [5], brain [6], spine [7, 8], hip [9, 10] and leg [11]. In the context
40 of this study the SSM is applied to hip images captured from an iDXA. This allows variations
41 in multiple geometric measures to be considered in concert thus describing the hip joint as a
42 whole. Each principal component, or mode of variation, describes a different aspect of hip
43 shape. By applying the SSM to a series of hip images from the same individual taken at

44 intervals allows the investigation of how the shape of the hip changes as a function of time.
45 In recent years, studies using SSM have shown that the resultant models can act as a
46 biomarker for musculoskeletal disorders of the hip, predicting hip fractures in osteoporotic
47 cohorts [10, 12-14] and incidence and progression of osteoarthritis, including total hip
48 replacement [9, 15-21].

49

50 Standardized Response Mean (SRM) (the mean difference between two measurements
51 divided by the standard deviation of the difference) is an effect size index that is frequently
52 used in medicine to gauge clinical change over time. Biomarkers with higher responsiveness
53 are desirable for clinical trials as this indicates trials could be shorter and more cost-
54 effective.

55

56 In this study we examine the change in hip shape mode scores over a 12 month period using
57 DXA images captured from a mixed-sex cohort with a range of OA severities at baseline.

58

59 **Materials and methods**

60 **Subject recruitment**

61 This is a prospective study using subjects recruited from the NHS Grampian Radiology
62 Information System (RIS). Computerised searches of the database identified subjects aged
63 >30 years who had undergone an anteroposterior pelvic radiograph or bilateral radiographs
64 of the hips in the previous 12 months. Radiographic reports were examined by a clinician to

65 assess suitability for the study. Subjects were excluded based on the following criteria:
66 surgical interventions (including total joint replacement and osteotomies), clear radiological
67 evidence of inflammatory arthritis, congenital / developmental dysplasia, avascular necrosis,
68 metabolic bone disease, or absence of a formal report on the RIS.

69

70 Following subject identification, letters were sent to the physician who initially referred the
71 subject for the radiograph to seek their help in recruiting the subject into the study (no
72 incentive was offered). The referring physician was asked to send an information pack to the
73 subject. Subjects were asked to complete a contact form and return it, to indicate interest in
74 participating in the study.

75

76 Written informed consent was obtained when subjects attended for bone density
77 assessment, in accordance with the declaration of Helsinki. The Grampian Research Ethics
78 Committees approved the study (ref. 06/S0801/116)

79

80 **Radiographic grading**

81 The radiographs of subjects who agreed to participate in the study were scored for OA
82 severity in both hips, by a single reader blinded to the clinical diagnosis, using the Kellgren-
83 Lawrence system (KLG) [1, 22]. Subjects were classified into control/doubtful OA according
84 to the most severe hip or the right hip if both hips scored the same KLG: KLG no more than 1
85 in either hip; moderate OA: KLG no more than 2; and severe OA: KLG of at least 3 in one hip

86 based on the KLG of their most severe joint. Subjects recruited into the study underwent
87 Dual Energy X-ray absorptiometry (DXA) scans (iDXA GE Lunar) of both hips on entry and
88 after 6 and 12 months.

89

90 **Statistical Shape Modelling**

91 The detail of the statistical shape modelling technique (SSM) used has been described
92 elsewhere [23]. In brief, Statistical Shape Modelling uses a set of “landmark points” to
93 describe the outline of an object. Each landmark point refers to the same location in every
94 image (for example the base of the lesser trochanter), allowing the variation in shape to be
95 measured across different images, and all the images from both hips at all three visits (0, 6
96 and 12-month time-points) were included in the model.

97

98 The landmark points were placed using the active shape modelling toolkit (Visual
99 Automation Limited, Manchester, UK), a software program that runs within MATLAB (The
100 Math Works Inc, Natick, United states) software environment, and analysed using custom
101 made software (SHAPE, Aberdeen University, Aberdeen, UK). The analysis performs a
102 Procrustes transformation, to remove effects of overall size, before applying principal
103 components analysis to generate a series of orthogonal modes that describe the variations
104 in shape within the set of images. The modes are scaled to have a mean of zero and unit
105 standard deviation for the whole image set. Each image is then given a score to describe
106 how far the shape lies from the mean shape for each mode.

107

108 In this study we built a 55-point SSM. This model included the proximal femur, part of the
109 acetabulum and osteophytes, allowing visualization of common radiographic features
110 observed in OA (Figure 1).

111

112 Figure 1 here

113

114 **Statistical Analysis**

115 Comparison between the groups at baseline was performed using one-way ANOVAs for
116 continuous variables (or Kruskal-Wallis ANOVA on Ranks if data were not normally
117 distributed determined using the Shapiro-Wilk test) and a Chi-squared test for sex balance.
118 To account for multiple measures from the same person (both hips, multiple visits)
119 Generalized Estimating Equations (GEE) were used to investigate the relationship between
120 shape, KLG and changes between visits after adjustment for age, sex and BMI (SPSS v22,
121 IBM corp). Both hips were included at each time-point and the dependent variable was the
122 mode of interest. Missing data were excluded. A separate GEE was run for each mode.
123 Variables analysed were Baseline KLG, Visit (in months), age at baseline, sex, BMI and the
124 interaction between visit and baseline KLG. An autoregressive correlation matrix (AR(1)) was
125 used. The distribution was set to 'normal' and link to 'identity'. This generates a measure of
126 the slope of the relationship, B, and its 95% confidence interval (CI) as well as a *P*-value,
127 which we used merely as a guide. We took results to be statistically significant when the
128 95% CI did not contain zero. Where statistically significant ($P < 0.05$) changes over time (with
129 visit) were observed, Standardised Response Means (SRM) and 95% confidence intervals

130 were calculated using the hip with the highest KLG for each person (Medcalc version15,
131 Ostend, Belgium). The SRM scales the difference between the means of two sequential
132 measurements by the standard deviation of the differences and enables measures of
133 different magnitudes to be compared. This allowed direct comparison of the responsiveness
134 with other published imaging measures used in OA.

135

136 **Results**

137 In total, 62 subjects (37 female and 25 male) were recruited into this study. At baseline, 14
138 hips were graded as KLG 0, 49 as KLG 1, 34 as KLG 2, 16 as KLG 3 and 11 as KLG 4. KLG was
139 determined from the baseline radiograph taken in the preceding 12 months. The average
140 time between radiograph and baseline iDXA scan was 225 ± 104 days. The mean time
141 between baseline and the 6-month DXA scans was 174 (17) days, between 6- and 12-month
142 DXA scans was 182 (18) days and for baseline DXA to 12-month DXA scan was 357 (30) days.
143 All three scans were obtained from 50 of the participants; eight had no 6-month DXA scan
144 and a further four did not receive a 12-month DXA scan. Table 1 shows the results of tests
145 for differences in the distribution of age, sex or BMI between the three severity groups
146 (control/doubtful, moderate and severe OA) at baseline. BMI was not normally distributed
147 (Shapiro-Wilk $P=0.034$), so Kruskal-Wallis ANOVA on Ranks was applied. No statistically
148 significant differences were observed for age ($P=0.37$), BMI ($P=0.084$) or sex ($P=0.067$).

149 Table 1 near here

150

151 A scree plot [24], showing the amount of variance in the model described by each mode,
152 was used to select the first 5 modes of variation. Mode 1 described 22.2% and mode 5 4.4%
153 of the variance. Together these 5 modes explained over 55% of the total variance and each
154 subsequent mode described less than 4% of the variance in the model.

155

156 These first 5 modes were analysed for association with KLG using GEE. After adjustment for
157 age, sex and BMI, statistically significant associations with KLG were observed in three
158 modes; mode 1 ($P < 0.0001$, $B = -0.29$ (95% CI = $-0.381, -0.19$)), mode 3 ($P = 0.001$, $B = 0.29$
159 (95% CI = $0.12, 0.46$)) and mode 4 ($P = 0.014$, $B = 0.18$ (95% CI = $0.04, 0.32$)). Of these, two
160 also showed significant differences with visit, mode 1 ($P < 0.0001$, $B = -0.036$ (95% CI = $-$
161 $0.051, -0.021$)) and mode 4 ($P < 0.0001$, $B = -0.037$ (95% CI = $-0.054, -0.019$)).

162

163 Examining these three modes further, by including interaction terms between KLG and visit,
164 showed significant interactions for modes 3 ($P = 0.009$, $B = -0.018$ (95% CI = $-0.032, -$
165 0.005)) and 4 ($P < 0.009$, $B = -0.022$ (95% CI = $-0.038, -0.005$)), but no interaction for mode
166 1 ($P = 0.26$). All three modes associated with KLG were significantly associated with sex and
167 modes 1 and 4 were also linked to BMI ($P \leq 0.05$). Two modes (Modes 2 and 5) were
168 associated with age ($P < 0.05$) but were not linked to any other input variables in the model.

169

170 Figure 2 shows the variations in shape described by modes 1, 3 and 4. Decreasing Mode 1
171 values (from +2sd to -2sd) show all the classical features of radiographic osteoarthritis:
172 increasing size of superior and inferior femoral head osteophytes, joint space narrowing and

173 deformation of the femoral head. In addition, there is also a reduction in neck shaft angle,
174 some uncovering of the femoral head and an increase in neck width. Increasing Mode 3
175 values (from -2sd to +2sd) were associated with superior and inferior femoral head
176 osteophytes and with uncovering of the femoral head. Increasing mode 4 values (from -2sd
177 to +2sd) were associated with growth of a superior femoral head osteophyte but not
178 inferior osteophytes and a decrease in neck shaft angle.

179

180 Figure 2 near here

181

182 The average mode 1 score decreased over the course of the 12-month follow-up and was
183 also found to have a negative association with KLG. Whilst the average mode 4 score also
184 decreased with visit this showed an inverse relationship with OA severity. Investigating the
185 effect size of these changes SRM values were calculated from the hip with the highest KLG
186 at baseline (used for severity grouping) over the first and second 6-month periods, then for
187 the full 12 months for modes 1,3 and 4 (Table 2). Further analysis by severity group (Table 3)
188 revealed the largest change in mode 1 was seen in those with moderate OA (12-month
189 SRM=-0.91 [-1.36, -0.55]) followed by those with severe OA (12-month SRM=-0.61 [-1.26, -
190 0.07]). In the control/doubtful OA group, mode 3 showed the largest changes (12-month
191 SRM=0.66 [0.26, 1.06]). Whilst in the severe group mode 4 was the most sensitive (12-
192 month SRM=-0.67 [-1.33, -0.10]).

193 Table 2 near here

194 Table 3 near here

195

196 **Discussion**

197 Data from this study demonstrate that SSM is a sensitive imaging biomarker that can
198 capture morphological changes in the hip over a period as short as 6 months, but more
199 reliably over 12 months. We observed a significant association between hip shape and OA
200 disease severity in three modes (Modes 1, 3 and 4) in this model. There was a rise in SRM
201 between 0-6 and 0-12 months when the cohort was analysed as a whole for each of the
202 modes. The SRM values reported here (-0.63, 0.44 and -0.40 for modes 1, 3 and 4
203 respectively over 12 months) are greater than those reported elsewhere in the literature for
204 a single measure over this timescale (reviewed in [25]), demonstrating improved
205 responsiveness to disease progression. Further, analysis by severity grouping revealed the
206 greatest change was observed over 12 months in the moderate OA group (Mode 1 SRM -
207 0.91). In addition, even in those patients categorised as having severe OA using the KLG
208 scoring system (KLG3 or 4) at baseline we were still able to demonstrate a progression over
209 12 months by shape changes captured by mode 1 (SRM -0.61) and mode 4 (SRM -0.67).
210 Interestingly, mode 3 appeared to detect changes over 12 months in individuals starting
211 with no or doubtful OA with a comparable SRM of 0.66. The variability between the SRMs
212 for the first and the second 6-month periods indicates that although changes may be
213 detected in six months this is not as reliable as over the full 12 months when the changes
214 are more consistent. Whilst there are, as yet, no DMOADs, new drugs that are in the early
215 stage of development are likely to work most effectively in mild to moderate OA subjects.
216 When therapies become available to slow radiological progression in OA SSM would then

217 provide a sensitive means of measuring these changes, especially in early and moderate
218 disease but also even in those with the most advanced OA.

219

220 Unsurprisingly, the shape model showed strong links with KLG, especially Mode 1 in which a
221 lower score was associated with the growth of osteophytes, femoral head and neck
222 deformation and joint space narrowing (Figure 2). One strength of the SSM approach is that
223 all of these features are detected simultaneously and a score assigned on a continuous
224 scale; they do not have to be assessed separately and graded on an ordinal scale. The
225 patterns observed by shape modes presented here match well with geometrical features
226 observed by other studies. For example, a decreased neck shaft angle, as seen in Mode 3
227 and Mode 4 was identified as a risk factor for OA by Doherty et al 2008 [26]. Deformation of
228 the femoral head, such as the non-spherical shape observed with low mode 1 scores has
229 also been identified previously in OA [26] as has the further deformation that occurs with
230 the progression of OA, with the femoral head becoming increasingly mushroom-shaped [15,
231 19, 20]. This sometimes-dramatic change in shape is included in the semi-quantitative
232 Kellgren-Lawrence grading system for moderate and severe cases. The uncovering of the
233 femoral head, as seen in mode 1 and 3 is a feature also captured in the Chingford cohort
234 using the Hip Morph software [27]. Statistical Shape Modelling allows quantification of
235 these effects and identifies feature that co-occur. This enables changes over periods as
236 short as 6 to 12 months to be measured (as shown here) or, as found previously, over a
237 period up to 5 years [19].

238

239 Joint space width (JSW) is the current gold standard for clinical trials assessing structural
240 progression of OA. Whilst much of the focus has been on the knee a number of studies have
241 investigated hip OA progression and these provide a useful effect size comparator. Few are
242 as good over a period as short as 6-12 months as those presented in this study. A systematic
243 review published in 2011 pooled 11 studies measuring minimum JSW in a meta-analysis
244 [25]. The overall SRM for the pooled data was 0.66. This is similar to the SRM for our mode 1
245 data, although the average time to follow-up was not reported for the pooled data and the
246 studies included ranged from 1-8 years, whereas our SRM for mode 1 was achieved after
247 just 1 year of follow-up. Data from individual studies produce SRMs that range from 1.75 to
248 0.27 [28-32]. Findings from a 1-year study in which subjects started with KLG 2 or 3,
249 reported a reduction in minimum JSW of 0.52 (0.49) mm (SRM 1.05) [33], which is
250 comparable with 0.91 observed in the current study when analysing those patients with a
251 KLG 2 at baseline. Traditionally, the terms 'small,' 'medium,' and 'large' were used by Cohen
252 to provide a qualitative assessment of the effect size. He pointed out, however, that these
253 should be treated as relative not only to each other but also to the research method being
254 employed in any given investigation [34]. Accordingly, we have used SRMs in order to be
255 able to compare our results with those from studies of JSW, which is measured on a
256 different scale.

257

258 We are not the only group to use DXA scans to predict OA progression, although others
259 have used DXA images to measure specific elements of hip geometry and morphometry [17,
260 35]. The use of DXA images has a number of key advantages over radiographs. The radiation
261 dose of a bilateral hip iDXA is ~20 μ Sv, compared with ~700 μ Sv for a bilateral hip

262 radiograph. In addition, patient positioning is also routinely more reproducible than in most
263 hip or pelvic radiography as position is important for accurate measurement of hip bone
264 mineral density, the most common use of DXA scanners. This minimizes possible effects due
265 to internal or external rotation. While the current modality of choice for OA imaging is MRI,
266 as it provides a 3D image, MRI scans are more expensive and require longer appointments
267 compared with DXA. In addition, modern DXA scanners, such as the iDXA, can take patients
268 weighing up to 450 lb, which is a distinct advantage in a disease where obesity is common;
269 the narrow aperture of an MRI scanner can make it difficult to scan patients whose BMI
270 exceeds $\sim 35 \text{ kg/m}^2$.

271

272 OA is gradually undergoing a paradigm shift away from being a disease of articular cartilage
273 to one of the whole joint or even the whole body. In this respect the use of SSM enables
274 changes across the whole joint, including contact alignment or coverage, anatomy, cartilage
275 thickness and osteophytes to be captured. This may contribute to its greater sensitivity to
276 subtle morphometric changes that appear to provide better biomarkers for incidence and
277 progression. Capturing these changes across the entire joint also paves the way to explore
278 further genetic factors affecting joint shape [36-38].

279

280 As with any study ours has limitations. We classified our patients into 3 groups based on
281 radiographic OA, which is not necessarily coincident with symptomatic clinical OA. Patients
282 recruited for this study were those who had undergone a pelvic or bilateral hip radiograph
283 in the previous 12 months and it is possible, therefore, that those in the control/doubtful

284 group, whilst not exhibiting radiographic OA, may have had clinically symptomatic OA. KLG
285 was determined from the baseline radiograph and these routine healthcare radiographs
286 were taken at some time in the preceding 12 months, as described above, which may have
287 affected group assignment. However, we have previously published data comparing KLG on
288 recruitment radiographs and baseline DXA images in this cohort that demonstrates that this
289 time gap had little effect on KLG repeatability [4], highlighting the lack of sensitivity of KLG
290 as a method for monitoring OA disease progression. It might also have been useful to have
291 taken matching radiographs at the 6-month time point as this would have allowed us to do a
292 head to head comparison of change over time DXA vs radiographs using SSM, this was not
293 done, however, in an effort to minimise radiation exposure in this cohort. Sex and BMI both
294 approached conventional standards for statistical significance ($0.10 > P > 0.05$) and it is
295 possible that a larger cohort might have led to dividing by sex or having to include BMI as a
296 covariate. In a recent study of a birth cohort of 1633 individuals imaged using DXA between
297 the ages of 60-64 years we found that all except one of the first ten modes generated in that
298 study differed between men and women [39] and that higher BMI throughout adulthood
299 and greater gains in BMI were associated with a shorter femoral neck and a wider and
300 flatter femoral head [40]. There was also an interaction between sex and BMI in the current
301 study with men having a greater BMI than women. This is something that can be explored in
302 future, larger, studies having shown in the current study that, at least in principle, it is
303 possible to detect changes over 12 months irrespective of sex or BMI.

304

305 In conclusion, we have demonstrated that SSM can capture changes in hip shape across the
306 entire joint over a period as short as 6 months, but more reliably, 12 months. This provides a

307 sensitive measure of hip OA progression. While similar results may be expected from
308 carefully positioned radiographic imaging, the use of DXA images demonstrates the utility of
309 this low-dose imaging modality for the assessment of OA.

310

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324

325 **Contributions**

326 Rebecca J Barr: Conception and design, Analysis and interpretation of the data, Drafting of
327 the article, Final approval of the article, Obtaining of funding

328

329 Jennifer S Gregory: Conception and design, Analysis and interpretation of the data, Drafting
330 of the article, Final approval of the article, Obtaining of funding

331

332 Kanako Yoshida, Critical revision of the article for important intellectual content, Final
333 approval of the article, Collection and assembly of data

334

335 Salvatore Alesci: Conception and design, Analysis and interpretation of the data, Critical
336 revision of the article for important intellectual content, Final approval of the article,
337 Obtaining of funding

338

339 Richard M Aspden: Conception and design, Critical revision of the article for important
340 intellectual content, Final approval of the article, Obtaining of funding, Integrity of the work
341 as a whole, from inception to finished article.

342

343 David M Reid: Conception and design, Critical revision of the article for important
344 intellectual content, Final approval of the article, Obtaining of funding

345

346 **Competing interests**

347 Dr Salvatore Alesci was an employee of Wyeth at the time of the study. All other authors
348 have no competing interests to declare.

349

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- 475

476 **Table 1.** Distribution of age, sex and BMI for each severity group comprising N individuals.
 477 Significance differences between groups were tested using Chi-Squared (sex), Kruskal-Wallis
 478 (BMI) and one-way ANOVA (age).

Severity Group	N	Sex	BMI	Age
		N female (%)	Median (25% - 75%)	Mean (sd)
Control/doubtful	20	15 (75%)	32.7 (29.2, 35.5)	64.9 (8.0)
Moderate	20	13 (65%)	29.1 (25.9, 32.7)	67.5 (7.2)
Severe	22	9 (40.9%)	28.5 (25.9, 33.9)	68.7 (10.5)
Total	62	37 (59.7%)	29.7 (27.3, 33.9)	67.1 (8.8)
P-value		0.067	0.084	0.37

479

480

481 **Table 2.** Standardized Response Means (SRMs) and 95% confidence intervals for modes 1, 3
482 and 4 for time periods 0-6 months, 6-12 months and 0-12 months.

483

	0-6 months	6-12 months	0-12 months
Mode 1	-0.41 [-0.68, -0.05]	-0.23 [-0.50, 0.05]	-0.63 [-0.88], -0.34]
Mode 3	0.23 [-0.04, 0.47]	0.35 [0.05, 0.64]	0.44 [0.19, 0.68]
Mode 4	-0.18 [-0.47, 0.08]	-0.44 [-0.73, -0.15]]	-0.40 [-0.71, -0.11]

484

485

486 **Table 3.** Standardized Response Means (SRMs) and 95% confidence intervals for modes 1, 3
 487 and 4 for time periods 0-6 months, 6-12 months and 0-12 months when data are split by
 488 severity (control/doubtful, moderate and severe OA). The number of individuals remaining
 489 in each group at each time point are given by N for the first mode.

490

		Control/doubtful	Moderate	Severe
Mode 1	0-6 months (N)	-0.11 [-0.61, 0.42] 19	-0.64 [-1.28, 0.06] 19	-0.43 [-1.00, 0.04] 16
	6-12 months (N)	-0.38 [-0.99, 0.13] 19	0.08 [-0.47, 0.59] 16	-0.33 [-0.84, 0.20] 15
	0-12 months (N)	-0.40 [-0.84, 0.07] 19	-0.91 [-1.36, -0.55] 16	-0.61 [-1.26, -0.07] 15
Mode 3	0-6 months	0.07 [-0.41, 0.52]	0.35 [-0.10, 0.78]	0.23 [-0.34, 0.71]
	6-12 months	0.68 [0.16, 1.19]	0.04 [-0.56, 0.48]	0.40 [-0.17, 0.99]
	0-12 months	0.66 [0.26, 1.06]	0.33 [-0.26, 0.74]	0.39 [-0.25, 0.76]
Mode 4	0-6 months	0.12 [-0.38, 0.60]	-0.27 [-0.77, 0.20]	-0.43 [-0.92, 0.17]
	6-12 months	-0.52 [-0.93, -0.03]	-0.33 [-0.79, 0.14]	-0.44 [-1.15, 0.16]
	0-12 months	-0.18 [-0.65, 0.34]	-0.39 [-0.99, 0.09]	-0.67 [-1.33, -0.10]

491

492

493 **Figure captions**

494 **Figure 1.** Design for the hip SSM, comprising the proximal femur, part of the acetabulum
495 and osteophytes. In the absence of the feature identified in colour, (e.g an osteophyte) the
496 points collapse back on to the primary outline.

497

498 **Figure 2.** Variations in hip shape identified by SSM. Mode 1 (a), Mode 3 (b) and Mode 4 (c)
499 showed significant associations with KLG. Solid red line indicates +2sd, dotted blue line
500 denotes -2sd.

501



SCRIPT

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