1   **Establishing outcome measures in early knee osteoarthritis**

2   Carolyn A Emery[1*], Jackie L Whittaker[2], Armaghan Mahmoudian[3], L Stefan Lohmander[4], Ewa M Roos[5], Kim

3   L Bennell[6], Clodagh M Toomey[7], Raylene A Reimer[8], Dylan Thompson[9], Janet L Ronsky[10], Gregor Kuntze[11],

4   David G Lloyd[12], Thomas Andriacchi[13], Martin Englund[14], Virginia B Kraus[15], Elena Losina[16], Sita Bierma-

5   Zeinstra[17,18], Jos Runhaar[18], George Peat[19], Frank P Luyten[20], Lynn Snyder-Mackler[21], May Arna Risberg[22],

6   Ali Mobasheri[23], Ali Guermazi[24], David J Hunter[25], Nigel K Arden[26]

7   *[1] Sport Injury Prevention Research Centre, Faculty of Kinesiology and Alberta Children's Hospital Research*

8   *Institute and McCaig Institute for Bone and Joint Health, Cumming School of Medicine, University of*

9   *Calgary, Calgary, Canada*

10   *[2] Department of Physical Therapy, Faculty of Rehabilitation Medicine, University of Alberta, Edmonton,*

11   *Canada*

12   *[3] Division of Rheumatology, Skeletal Biology & Engineering Research Center, University Hospitals KU*

13   *Leuven, Belgium*

14   *[4] Department of Clinical Sciences Lund, Orthopaedics, Lund University, Lund, Sweden*

15   *[5] Department of Sports and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark*

16   *[6] Centre for Health, Exercise and Sports Medicine, University of Melbourne, Melbourne, Australia*

17   *[7] Sport Injury Prevention Research Centre, Faculty of Kinesiology University of Calgary, Calgary, Canada*

18   *[8] Faculty of Kinesiology and Department of Biochemistry and Molecular Biology, University of Calgary,*

19   *Calgary, Canada*

20   *[9] Department for Health, University of Bath, Bath, UK*

21   *[10] Schulich School of Engineering, Faculty of Kinesiology, and McCaig Institute for Bone and Joint Health,*

22   *Cumming School of Medicine, University of Calgary, Calgary, Canada*

1

23 [11] *Sport Injury Prevention Research Centre, Faculty of Kinesiology and Alberta Children's Hospital*

24 *Research Institute and McCaig Institute for Bone and Joint Health, Cumming School of Medicine,*

25 *University of Calgary, Calgary, Canada*

26 [12] *Gold Coast Centre for Orthopaedic Research, Engineering and Education (GCORE), Menzies Health*

27 *Institute Queensland, Griffith University, Australia*

28 [13] *Department of Mechanical Engineering and Department of Orthopedic Surgery, Stanford University,*

29 *Stanford CA, Palo Alto Veterans Affairs Health Care System, Palo Alto, CA, USA*

30 [14] *Clinical Epidemiology Unit, Orthopedics, Department of Clinical Sciences Lund, Lund University, Lund,*

31 *Sweden*

32 [15] *Duke Molecular Physiology Institute and Division of Rheumatology, Department of Medicine, Duke*

33 *University School of Medicine, Durham, NC, USA*

34 [16] *The Orthopaedic and Arthritis Center for Outcomes Research, Brigham and Women's Hospital, Harvard*

35 *Medical School and Boston University School of Public Health, Boston, MA USA*

36 [17] *Department of Orthopaedics, Erasmus MC - University Medical Center Rotterdam, The Netherlands; D-*

37 *BOARD Consortium, European Commission Framework 7 programme*

38 [18] *Department of General Practice, Erasmus MC - University Medical Center Rotterdam, The Netherlands;*

39 *D-BOARD Consortium, European Commission Framework 7 programme*

40 [19] *Arthritis Research UK Primary Care Centre, Research Institute for Primary Care & Health Sciences, Keele*

41 *University, Staffordshire, UK*

42 [20] *Division of Rheumatology, Skeletal Biology & Engineering Research Center, University Hospitals KU*

43 *Leuven, Belgium*

44   [21]*Departments of Physical Therapy and Biomedical Engineering, STAR Health, University of Delaware,*

45   *Newark, Delaware, USA*

46   [22]*Norwegian Research Center for Active Rehabilitation, Department of Sports medicine, Norwegian School*

47   *Sport Sciences and Division of Orthopedic Surgery, Oslo University Hospital, Oslo, Norway*

48   [23]*Department of Regenerative Medicine, State Research Institute Centre for Innovative Medicine, Vilnius,*

49   *Republic of Lithuania; Faculty of Health and Medical Sciences, University of Surrey, Guildford, Surrey,*

50   *UK; Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis; Pain Centre, Medical Research*

51   *Council and Arthritis Research UK Centre for Musculoskeletal Ageing Research; Queen's Medical Centre,*

52   *Nottingham, UK; D-BOARD Consortium, European Commission Framework 7 programme, APPROACH*

53   *Consortium, European Commission Innovative Medicines Initiative (IMI)*

54   [24]*Boston University School of Medicine, Boston, USA*

55   [25]*Institute of Bone and Joint Research, Kolling Institute, University of Sydney and Rheumatology*

56   *Department, Royal North Shore Hospital, Sydney, Australia*

57   [26]*Centre for Sport, Exercise and Osteoarthritis, VersusArthritis, Oxford University, Oxford, UK*

58   Email: caemery@ucalgary.ca

59

60

61

62   **Abstract**

63   The classification and monitoring of individuals with early OA is an important strategy for the design and

64   evaluation of therapeutic interventions. Such an approach requires the identification of appropriate

65   outcomes measures. Potential outcome measures for early OA include patient-reported outcomes (such

3

66 as measures of pain, function or quality of life), features of clinical examination (such as joint line

67 tenderness and crepitus (that is, grating and crackling sounds)), objective measures of physical function,

68 levels of physical activity, movement biomechanics, structural assessments such as magnetic resonance

69 imaging (MRI) and body fluid biomarkers. Patient characteristics such as adiposity and biomechanics of

70 the knee could also have relevance to early OA. Importantly, future research is needed to enable the

71 selection of outcome measures that are feasible, reliable, and validated in those at risk of OA and an early

72 knee OA population. In this Perspectives paper, potential outcome measures of individuals with early

73 symptomatic knee osteoarthritis (OA) are discussed, including those that could be of use in clinical practice

74 as well as research settings.

75

76 **[H1] Introduction**

77 Osteoarthritis (OA) is a leading cause of chronic pain, disability, and health care utilization, with knee OA

78 contributing the greatest burden[1-4]. OA is associated with increased rates of comorbidity (for example,

79 obesity and heart disease)[1] and ranks the 13th [2] most burdensome amongst all forms of disability world-

80 wide. The incidence and burden of OA is considerable and growing[3, 5]. Therefore, a shift in the treatment

81 approach is needed from treating patients once they have established OA to a proactive approach that

82 focuses on mitigating risk factors. The classification and monitoring of early OA, on a trajectory from

83 normal to symptomatic and/or radiographic OA, would provide an opportunity in clinical practice and

84 research for the development and evaluation of interventions to prevent or slow down the disease process

85 at a time it is probably more amenable to modification.

86 Although the definition of early OA and appropriate outcomes are under development OA is probably

87 heterogeneous in terms of its presentation and progression. Knee OA might progress slowly over a period

88 of ten or more years, rapidly, or not at all[6]. Predicting the development and progression of disease through

89 identifying risk factors and mechanisms of OA is important in chronic disease management to inform

90 targeted OA prevention and treatment strategies. This strategy is difficult because of the heterogeneous

91   presentation of OA; however, the availability of increasingly sophisticated statistical and computational

92   methods, microsimulation modelling, and large population-based cohort studies make this approach

93   increasingly viable. For example, widely-used online prediction tools are now available for evaluating

94   future risk of osteoporotic fractures and for guiding clinicians in preventive management of osteoporosis[7-

95   9]. Comparable reliable and validated outcomes for early OA will inform the evaluation of risk factors for

96   the progression of early OA. More than one set of risk factors and models will probably be needed to

97   predict early OA in the future. The Rotterdam and Chingford studies (two prospective population-based

98   studies) have demonstrated an ability to predict incident radiographic knee OA using a combination of

99   clinical, genetic, and radiographic factors[10]. When performing risk assessment and creating a predictive

100   model for early knee OA, many aspects need to be considered: the definitions of the outcome and

101   prognostic factors; the duration of the clinically relevant prediction period; and the setting in which the

102   risk prediction tool will be used (for example, primary care, secondary care or a research setting). For

103   instance, expensive and intensive predictive tools such as MRI scans and biomarkers might be restricted

104   to secondary care and/or a research setting.

105   In this Perspectives article, we highlight considerations for best practice in the selection of outcome

106   measures for use in clinical and research settings to evaluate patients at initial presentation of early knee

107   OA across different outcome domains: patient-reported outcomes, clinical examination, physical function,

108   adiposity, physical activity, nutrition, biomechanical outcomes, imaging features and biochemical markers

109   [11]. We suggest outcome measures that could be considered for use in individuals with early knee OA in

110   clinical care and research settings using published evidence (primarily from post-traumatic and established

111   OA populations), emerging evidence (ongoing studies), and clinical expertise (Box 1). The outcome

112   measures highlighted are relevant to individuals that are at risk of OA and fit the provisional criteria for

113   early knee OA based on patient reported outcomes of pain and function, together with clinical signs (joint

114   line tenderness or crepitus) and a radiographic Kellgren-Lawrence (KL) grade of 0-1[12]. Although proposed

115   as important evidence-informed clinical outcome measures, these outcome measures will require

116   additional validation and possible modification to suit local primary care and other healthcare settings, as

117   well as periodical updates.

118

119   **Patient-reported outcomes**

120   Patient-reported outcomes are any report of a patient's health status that comes directly from the patient

121   without interpretation by others (for example, the clinician). These measures commonly take the form of

122   a questionnaire. Most relevant patient-reported outcome measures have been developed to either assess

123   individuals with a knee injury (for example, International Knee Documentation Committee 2000

124   (IKDC2000)) or established OA (for example, Western Ontario and McMaster Osteoarthritis Index

125   (WOMAC)); although, one questionnaire has been developed to cover the full spectrum from injury to

126   established OA (the Knee Injury and Osteoarthritis Outcome Score (KOOS)). The relative merits of these

127   and other available instruments that measure self-reported pain, function, and quality of life have been

128   the subject of previous reviews[13, 14]. Today measures, such as PROMIS, are often developed using

129   computer adaptive strategies which may also prove to be relevant for use in people with early OA[15]. Many

130   of the considerations that influence the choice of measure in established OA (for example, respondent

131   burden, cost or availability) apply also in early OA.

132   Ultra-brief (one or two domains) unidimensional generic measures, such as the 11-point Numerical Rating

133   Scale (NRS-11), the 36-Item short form health survey (SF-36) bodily pain scale (SF-BP 36), have been

134   recommended in previous reviews for established OA[16] and are probably applicable also in early OA.

135   However, the disadvantage of generic health status measures is a restricted view of the pain character and

136   intensity[16, 17], which is probably inappropriate based on emerging evidence from qualitative studies in

137   patients with early knee OA[18-20]. For instance, these patients report that their initial symptoms can be

138   experienced as 'an awareness' of the knee, loss of confidence, or needing to 'be careful' as opposed to

139   'pain'. The KOOS knee-related quality of life subscale includes consideration of questions on these aspects

140   [14,15]. Further, reporting OA pain as 'constant' or 'present on most days' might give floor effects (i.e., most

141   individuals may report at the lower end of the scale) in early OA as these patients often report episodic

142   and intermittent pain with certain activities. For example, pain during ascending or descending stairs

143   seemed to be the earliest functional difficulty reported in the OA initiative[21]. Accordingly, the intermittent

144   and constant assessment of pain score (ICOAP) questionnaire, which includes a subscale on intermittent

145   symptoms, has an increasing amount of evidence supporting its' reliability and validity.[22]

146   Another important consideration is that the early phase of knee OA is often associated with the emergence

147   of adaptive behaviour. Symptom frequency and intensity might be minimized through the selection of

148   behaviours (for example, performing some activities less often), optimization of behaviours (for example,

149   advanced planning of activities, including anticipatory analgesic use), and compensatory adaptations (for

150   example, modifying the way activities are performed)[23]. Therefore, consideration of adaptive behaviour is

151   a legitimate topic for outcome measurement in early OA[24], an example of which is the Questionnaire to

152   Identify Knee Symptoms (QuIKS). QuIKS includes questions such as "I am considering stopping a favorite

153   activity due to my knees" and "I am considering changing my exercise routine due to my knee problems"[25]

154   The KOOS was developed for self-reporting of patient-relevant outcomes across the lifespan, from time of

155   knee injury and potential knee OA onset to severe OA[26-29]. In five separate subscales this tool assesses

156   perceived pain and other symptoms (e.g., stiffness, grinding, catching), perceived difficulty with function

157   during daily life and sport and recreational activities, and knee-related quality of life. The KOOS

158   measurement properties have been reported in studies of young, middle-aged, and elderly groups with

159   knee injury or OA, and across the spectrum of treatments[14]. A comprehensive literature search identified

160   37 eligible papers evaluating KOOS measurement properties in participants with knee injuries and/or

161   osteoarthritis (OA) and found that KOOS demonstrates adequate content validity, internal consistency,

162   test-retest reliability, construct validity and responsiveness for age- and condition-relevant subscales[14].The

163   KOOS is feasible to administer electronically and in paper form and KOOS scoring instructions and

164 population-based KOOS reference data are available. In addition, longitudinal KOOS data have been

165 collected from more than 100,000 patients in surgical registries of anterior cruciate ligament

166 reconstruction and knee replacement facilitating comparisons to many different populations[30, 31]. In

167 addition, for the interested researcher, KOOS data are freely available and collected from the cohort of

168 patients who are at increased risk of OA and the cohort of patients with established disease from the NIH-

169 sponsored OA Initiative[32]. The OA initiative also collects a wide range of other self-reported, clinical and

170 imaging data[32]. The "at risk " cohort includes people with symptoms and two or more risk factors (including

171 knee injury) but without radiographic OA[32].

172 The ICOAP was designed to evaluate the pain experience in people with OA. It includes pain intensity,

173 frequency, and impact on mood, sleep and quality of life. It is intended to be used alongside a measure of

174 physical function[22]. OA-specific measures developed for more advanced OA cannot be assumed to have

175 adequate psychometric properties when applied to early OA. Yet, the requirement for adequate

176 performance in early OA must be balanced against the benefits for a coherent evidence base that comes

177 from using common measures across the spectrum from early to advanced OA. Of existing measures, the

178 KOOS and ICOAP seem to best strike this balance and are therefore strong candidates for evaluating early

179 knee OA (Box 1), particularly as these instruments focus on different aspects; both have the advantage of

180 being freely available. Published reviews of the psychometric properties of these two measures require

181 systematic updating with specific attention to their performance in early OA.

182

183 **Clinical examination outcomes**

184 Clinical examination outcomes are relevant in research and are easy to perform in primary care. Joint line

185 tenderness (tibiofemoral and/or patellofemoral joint lines) at baseline was suggested to be a strong

186 predictor of five-year pain progression (moderate progression adjusted OR=3.9 (95% CI; 2.3 - 6.6)[33] in the

187 CHECK cohort (n=705) that included patients with newly onset knee pain or stiffness[34]. Several studies

8

188 have evaluated the ability of physical signs to predict the clinical onset of structural radiographic OA in

189 patients with an increased risk of OA [33-37]. Data from the HONEUR Study, which included 549 participants

190 who were recruited at the first presentation of knee pain in primary care, suggested that joint line

191 tenderness, crepitus (that is, grating, crackling, popping sounds), pain with passive flexion, and a self-

192 reported swollen knee predicted incident radiographic tibiofemoral knee OA after 6 years[35]. Using MRI

193 features of knee OA as an outcome measure, data from the general population Rotterdam Study showed

194 that joint line tenderness together with the 'feeling of giving way' were associated with the incidence of

195 tibiofemoral knee OA, whereas crepitus was identified as a good predictor of patellofemoral OA[36, 37].

196 Easily assessable measures from physical examination might be associated with future OA development,

197 including joint line tenderness and crepitus, even in the absence of radiologic findings of OA (Box 1).

198 Clinical examination of these features had good inter-observer reliability in a population with evident knee

199 osteoarthritis if a standardised approach to such assessment is used[38]. However, these clinical assessment

200 components require further examination of reliability and validation for research settings in early knee OA

201 and standardization for use in clinical settings.

202 **Physical function outcomes**

203 Given that the early pre-radiographic stage of OA is associated with intermittent symptoms and adaptive

204 physical behaviour, the clinical evaluation of patients with, or at risk of, early knee OA should incorporate

205 robust outcome measures of physical function[39]. Currently, no consensus exists regarding which outcomes

206 are most relevant for use in this population. For the purposes of this Perspective article, physical function

207 is operationally defined as 'physiological functions' or 'the ability to move around and to perform daily

208 activities' that can be classified as 'body functions and structure' or 'activities and participation',

209 respectively, using the World Health Organization International Classification of Functioning, Disability and

210 Health (ICF) model[40]. As physical function is multi-dimensional, both performance-based and physical

211 impairment measures (which might require specialized pieces of equipment and raters) are discussed in

212 this section. Emerging evidence suggest that some of these outcome measures might be suitable for the

213 evaluation of early OA and those at risk of OA (Table 1)[41-46].

214 A range of performance-based measures are available although the degree to which their measurement properties

215 are established and the range of populations they have been used in varies (Table 1). Measures that have

216 undergone fairly extensive investigation include the Single Leg Hop for distance test[43, 44, 47-50], the Cross Hop for

217 distance[43, 47-50], the 6-meter Timed Hop Test[43, 47-50], the Star Excursion and similar Y-balance test[44, 51-55], the 30-

218 second Chair Sit-to-Stand Test[56-58], and the 6-minute walk test[41, 42], while there is emerging evidence for the Vertical

219 Drop Jump [44, 59], the Single Leg Squat [44, 60-62], Unipedal Dynamic Balance test [44, 63] and 20-meter Shuttle Run[44, 64]. The

220 most commonly reported outcome of physical impairment is quadriceps muscle strength[44, 47, 48, 51, 65], however,

221 there might also be value in considering the strength of other lower extremity muscles including the hamstring, hip

222 abductor and hip adductor muscle.; although, insufficient information is available to advocate for specific

223 contraction mode (i.e., isotonic, isokinetic or isometric) or type (i.e., concentric or eccentric).

224 Because of floor and ceiling effects (i.e., most individuals report a minimum – floor, or maximum – ceiling

225 score), separate measures are required to cover the wide range of ages and abilities of patients with early

226 knee OA in both clinical and research settings. Functional outcomes that should be considered for use in

227 research and in clinical physical and exercise therapy practice based on their measurement properties and

228 ability to span the full spectrum of patient age and abilities include the Single Leg Hop for distance, 30-

229 second Chair Sit-to-Stand Test, 6-minute walk test and a quadriceps strength measure. The performance-

230 based outcomes should be administered in a standardized, validated and reproducible fashion to enable

231 detection of change over time; video demonstrations and explicit instructions for standardized testing are

232 available online (see related links). Further research validating functional outcomes in 'at risk' (e.g., intra-

233 articular knee injury, obesity, varus/valgus alignment abnormality) and 'early-OA' populations is required

234 and this research should inform the periodic updating of these suggested functional outcomes.

235

236 **Modifiable lifestyle-related outcomes**

237 The presence of modifiable risk factors related to lifestyle, such as obesity, dietary inadequacies, and

238 physical inactivity might lead to accelerated disease onset and progression through a combination of

239 mechanical and systemic mechanisms[66]. Identifying these modifiable risk factors in early knee OA is

240 important for the prevention of OA.

241 Several measures of adiposity or weight have been studied in established OA, but less so in early OA. These

242 include BMI, waist-height ratio (WHR) and waist circumference[67-71]. The location of fat depots influences

243 their metabolic and inflammatory potential and therefore may be important considerations. A high waist-

244 height ratio or waist circumference (indicative of abdominal adiposity) were associated with an increased

245 risk of OA progression[71]; however, neither outcome was associated with the loss of tibial or patellar

246 cartilage volume or defects in adults in the community with pre-radiographic OA[72, 73]. To detect a change

247 in visceral fat at this early stage, more accurate assessments of abdominal adiposity are needed.

248 Measurements of fat mass (kg), percentage fat mass (percentage of total mass) and fat mass index (FMI;

249 fat mass/height^2), can be obtained using dual-energy x-ray absorptiometry or bioelectrical impedance

250 analysis, hence permitting a direct measure of adiposity[74]. Total fat mass is positively associated with an

251 increased risk of knee cartilage defects and the presence of bone marrow lesions in healthy individuals

252 (aged 25-60 years)[75] and medial tibiofemoral cartilage volume loss over 2-10 years in adults aged 51-81

253 years[76, 77]. A systematic review reported moderate evidence for the relationship between obesity (that is,

254 increasing weight, BMI or total body fat mass) and the presence of bone marrow lesions in the knee in

255 individuals with OA[70]. In addition to contributing to an increased mechanical load, adiposity is thought to

256 have a metabolic and pro-inflammatory function in OA; therefore, a direct measure of adiposity (fat mass,

257 percentage fat mass or FMI) rather than BMI, might be more useful in the assessment of early-stage OA[78-

258 81].

259 Physical activity is a modifiable outcome that might delay the onset of functional limitation, prevent

260 obesity, and is essential for normal joint health[82]. In addition, physical activity can reduce pain and

261 disability among individuals with OA and increase their physical performance and self-efficacy[83-85]. Light or

262 moderate intensity physical activity might protect against the onset of disability related to symptomatic

263 OA, whereas a sedentary lifestyle or levels of strenuous physical activity is considered a risk factor[86-88].

264 Many variations of self-reported measures of physical activity exist including global or short recall

265 questionnaires, although most have limited accuracy[86-88]. Wearable monitors that measure body motion

266 can be used to assess physical activity and energy expenditure. The most commonly used sensor, validated

267 across multiple populations, is an accelerometer (for example, Actigraph)[89], which captures frequency,

268 intensity, and duration of physical activity in a time-stamped manner. The large selection of off-the-shelf

269 accelerometers, often contained in mobile phones, might be more suitable in a primary care setting to

270 measure physical activity as they are less expensive, easier to use and widely available[90, 91]. Most

271 accelerometers, however, are not validated to measure cycling or swimming. In general, objective

272 measures of physical activity such as accelerometer outcomes compared with self-reporting have stronger

273 relationships with function in OA[92] and are a more accurate assessment of physical activity and sedentary

274 lifestyle.

275 Nutrition interventions such as weight loss[93, 94] are lifestyle-related changes that can potentially improve

276 OA symptoms. Beyond the link between obesity and knee OA (and therefore the important contribution

277 of weight loss)[95, 96], the contribution of nutritional factors is an emerging and important area of research,

278 although limited clinical evidence is available to date. For example, low dietary intakes of fibre[97] or omega-

279 3 polyunsaturated fatty acids[98], and high fat diets[99] are risk factors for OA and/or worsening of pain in OA

280 and might therefore warrant monitoring in early OA. Many of the nutrients or dietary patterns tested to

281 date probably contribute to pathology via alterations in body weight or inflammation, although the direct

282 effects of these factors requires further investigation. The tools to monitor dietary intake are numerous

283 (for example, the Food Frequency Questionnaire (FFQ), 24-hour dietary recall (either the paper-based or

284 web-based automated self-administered 24-hour dietary recall (ASA24) assessment tools[100]) and the 3-

285   day or 7-day weighed food record) and need to be assessed for each clinical or research setting. In addition,

286   tools to assess adherence to diets that reduce inflammation such as the Mediterranean Diet Adherence

287   Screener[101] might also warrant use in future.

288   Hence, objective measures of adiposity are desirable. BMI is a useful outcome measure for assessing

289   adiposity in a primary clinical setting because of its familiarity, validity, and reference ranges. However,

290   BMI has limitations for use in young athletes. Although weight loss can improve OA symptoms, further

291   research is needed to identify a means of assessing important OA-related nutritional factors. Assessment

292   of physical activity using a validated accelerometer, to accurately capture activity through each domain

293   and intensity, is a promising area that requires future study.

294

295   **Biomechanical outcomes**

296   Biomechanical outcomes are measures of joint mechanics typically collected in a research setting, but

297   sometimes taken in a primary care setting. Joint mechanics can be employed to assess OA severity, but

298   also for understanding the causes of OA onset and progression. For example, altered joint mechanics

299   following knee injury might contribute to the onset and development of post-traumatic OA[39]. Indirect

300   evidence to support this concept comes from observations of altered joint movement, loading, and muscle

301   activation patterns following injury[102-107], with radiographic knee OA (KL≥2)[108-110], with aging[111, 112] and pre

302   and post joint arthroplasty[113-115]. Abnormal joint alignment[116, 117], alteration of the external knee adduction

303   moment (KAM) and increased varus alignment are often regarded as indicators of altered joint mechanics

304   associated with increased OA severity[110]. However, joint mechanics in OA might also change because of

305   other factors including loss of dynamic joint stability[118, 119], muscle atrophy[120], neuromuscular inhibition[121],

306   muscle weakness,[122-124] and compensatory muscle activation mechanisms[108, 109, 114]. These changes might

307   alter cartilage loading and contact mechanics. Indeed, some studies indicate changes in tibiofemoral

308   cartilage contact locations[39, 125], elongated path lengths[126], force magnitudes[103, 127, 128], and deformations[125,

309   [126] are associated with OA onset and progression. In turn, OA progression might be caused by progressive

310   degradation of cartilage through interactions of articular movement and cartilage loading abnormalities,

311   chronic inflammation, resultant tissue remodelling, and other OA risk factors by increasing the

312   susceptibility of cartilage and subchondral bone to damage and degradation at regions inadequately

313   adapted to these altered loads[125, 129-133]. Over time, this process might result in altered cartilage thicknesses

314   and clinically relevant cartilage thinning in different regions of the articular cartilage surfaces. To verify

315   this mechanism, longitudinal data are needed of the joint mechanics, cartilage thickness, and cartilage

316   structure and integrity in OA[134, 135]. Integration of this information with other risk factors for OA-related

317   changes might inform the development of novel patient-specific, diagnostic or predictive models to aid in

318   early patient screening, intervention efficacy monitoring, and the development of new therapeutics[127, 128,

319   130, 136, 137]. Armed with these data and models, new wearable monitors might enable biomechanical

320   outcomes assessment in the clinic and community[131-133, 138, 139], and might provide the possibility of

321   developing and monitoring personalized treatment plans.

322   Presently, the joint range of motion is a suggested measure that could be collected in a primary care setting

323   to assess OA severity. The other biomechanical outcomes mentioned above (e.g., KAM, kinematics,

324   electromyography, cartilage loading) although used to understand the mechanisms of OA progression

325   and currently not feasibly collected in most clinical settings, are an important component for consideration

326   in research settings to inform orthotics design, exercise interventions, bracing, and surgical interventions.

327   In the future, validated wearable monitors might help assess biomechanical outcomes of early

328   interventions in the clinic and community. Evidence suggests that outcome measures are not independent

329   but rather variation in one outcome measure (for example, biomechanical outcomes) can influence the

330   quantitative state of another measure (for example, biomarkers or imaging outcomes)[140-144]. Thus, future

331   research should consider the interaction between different outcome measures to potentially increase the

332   sensitivity of detecting early OA[129, 141].

333

Imaging outcomes

Osteoarthritis is a complex syndrome that at the local level, is best characterised as a whole joint disease involving multiple tissue pathologies. In attempting to characterise and monitor the variety of OA structural components a number of different imaging modalities have been used-the most common amongst these being x-ray, ultrasound and MRI. This section will predominantly focus on plain radiography and MRI, as ultrasound has a number of limitations that have constrained its development and validity in this area including observer dependency and an inability to adequately image weight-bearing portions of the joint.

Radiographic features of OA are generally classified by the Kellgren and Lawrence (KL) grading system[145] and include joint space narrowing, osteophyte formation, sclerosis, and deformity of bony contours[146]. Minimum radiographic joint space width (JSW) is the gold standard recommended by the FDA for detecting structural changes in patients with knee OA in clinical trials. Standardized measures of radiographic positioning and fixed location JSW can reach the same degree of responsiveness as quantitative measures of cartilage thickness on MRI [147]. However, radiographic features such as loss of joint space, sclerosis, and deformity of bone are associated with late-stage OA and are preceded and detected with greater sensitivity by MRI.

Conventional MRI enables the evaluation of morphological changes related to early OA, including but not limited to cartilage damage, meniscal damage, synovitis, presence of BMLs, and ligamentous damage. In one study of patients with knee pain (n=255, age 40-79 years), BMLs were present in 11% of individuals without radiographic OA (KL = 0), 38% of individuals with pre-radiographic OA (KL = 1) and 71% of individuals with radiographic OA (KL >2)[148, 149]. Similarly, 42% of patients with a diagnosis of symptomatic OA without radiographic features (KL < 2) had BMLs and 57% had cartilage loss[150]. Although a paucity of data exists regarding the timeline of structural changes in the period between a joint injury sustained in

15

357 youth and the onset of clinical post-traumatic OA, advanced MRI techniques have been used to detect

358 subtle cartilage damage at the time of ACL injury[151]. Furthermore, macroscopic cartilaginous changes, the

359 presence of BMLs, and bone morpholology changes might be detectable by conventional MRI techniques

360 as early as two years post ACL reconstruction or other intra-articular knee injury (and potentially before

361 the development of radiographic OA)[6, 152-155].

362 In 2011, a definition of MRI-defined OA was proposed to facilitate earlier detection of OA (Box 2)[156, 157]. In

363 one study of patients who had undergone anterior cruciate ligament (ACL) reconstruction, 19% and 17%

364 of the participants met the MRI criteria for tibiofemoral and patellofemoral OA, respectively, at 1 year[158].

365 Importantly, some of the changes included in this criteria are undetectable by radiography (i.e. cartilage

366 thickness, bone marrow lesions). Different methodologies can be used to measure structural changes in

367 the knee by MRI including the use of semi-quantitative measures (such as the MRI Osteoarthritis Knee

368 Score (MOAKS)), quantitative measures (including cartilage thickness, bone marrow lesion volume,

369 effusion-synovitis volume and meniscal extrusion) and measures obtained using compositional imaging

370 modalities of cartilage (including T2 mapping, T1ρ mapping, delayed gadolinium-enhanced MRI of cartilage

371 (dGEMRIC), sodium MRI and glycosaminoglycan chemical exchange saturation transfer (gagCEST)) which

372 measure cartilage composition and quality[159]. Semiquantitative MRI evaluation can be performed using

373 several available scoring systems such as the MRI Osteoarthritis Knee Score (MOAKS) and the Anterior

374 Cruciate Ligament Osteoarthritis Score (ACLOAS)[148, 160]. For synovitis assessment, contrast-enhanced MRI

375 should be used and semi-quantitative scoring systems based on contrast-enhanced MRI are available to

376 enable clear delineation of the synovium from effusion[161]. In population-based studies, a high proportion

377 of radiographically normal knees have osteophytes and cartilage damage detectable by MRI illustrating

378 the greater sensitivity of MRI as compared to radiography[149]. However, it also highlights the challenge of

379 what is to be regarded as osteoarthritic disease and what is part of a normally ageing joint[162]. The link

380 between anatomical evidence of OA and patients' symptoms and function is still rather weak[163, 164].

381 Ultimately, the presence of these findings on MRI require validation by longitudinal follow-up studies to

382 identify their association with subsequent illness related to OA (alteration of patient function and

383 symptoms)[165] to avoid over-diagnosis because of incidental MRI findings[148, 149, 166-168]. Notably, the

384 distinction between pathology and normal features of the ageing joint is unclear and further research to

385 elucidate the importance of MRI findings in early knee OA is warranted.

386 Hence, the utility of plain radiography in early OA is limited as only relatively late OA changes are

387 detectable. As technology improves, assessing changes in bone shape or trabecular bone texture of sub-

388 chondral bone might be of use. MRI has superior sensitivity to change and validity in the context of early

389 OA. Although not appropriate for all primary care settings because of the high cost and risk of over-

390 diagnosis, MRI is a critical component of ongoing outcome validation research in early knee OA.

391

392 **Biomarker outcomes**

393 Some laboratory OA biomarkers detectable in blood, urine or synovial fluid are associated with or

394 predictive of incident radiographic knee OA. Biomarkers of joint tissue turnover can reflect disease-

395 relevant biological activity that might not otherwise be apparent before structural changes are detectable

396 by MRI or plain radiography. Ideally, biomarkers of early OA must clearly differentiate between normal

397 (physiological) and pathological tissue turnover as well as between the early stages of the disease and

398 more advanced joint destruction. The biomarkers must also be unaffected by other disorders and be easily

399 measured in a clinical setting[169]. Biomarkers of early OA might also be used to identify pre-radiographic

400 changes at the molecular level and facilitate OA drug discovery, and potentially enable a more rational and

401 personalized approach to healthcare OA management by prompting earlier and more targeted treatment

402 [170].

403 Studies of incident OA have identified some of the earliest molecular abnormalities associated with OA

404 and therefore provide biomarker candidates for early OA identification. 10 years prior to radiographic

17

405 hand or knee OA, four serum proteins (matrix metalloproteinase-7, IL-15, plasminogen activator

406 inhibitor-1 and soluble vascular adhesion protein-1) were altered in a cohort of patients with OA

407 compared with healthy individuals[171]. Similarly, serum COMP (sCOMP) and hyaluronan concentrations

408 could predict[172] incident knee joint space narrowing and osteophyte (sCOMP) formation 7 years later in

409 another patient cohort. In another study, incident radiographic knee OA over ten years was positively

410 predicted by serum COMP concentration (based on KL scores) at baseline but negatively predicted by

411 serum aggrecan concentration[173]. Furthermore, mean baseline serum osteocalcin concentrations levels

412 are associated with 3-year incident radiographic hand OA (KL >2) but not knee OA in pre-menopausal

413 and peri-menopausal women[174]. Bioactive lipids are also potential biomarkers of pain and inflammation

414 [175] and metabolomics has been used to identify metabolic profiles that can differentiate between

415 synovium samples from patients with OA and healthy individuals[176].

416 In 2006, the NIH-funded OA Biomarkers Network and the OARSI Clinical Trials Biomarkers Working group

417 proposed a new classification system for OA biomarkers termed BIPEDS[177, 178]. The purpose of this

418 classification was to clarify the intended primary use of the biomarker to reflect Burden of OA disease,

419 Investigative, Prognostic for OA development, Efficacy of OA intervention, Diagnostic for OA and Safety of

420 intervention biomarkers) classification system for OA biomarkers[172,173]. However, a systematic review

421 performed in 2010 concluded that individual biochemical markers and categories of biochemical markers,

422 including their nature, origin and metabolism, need further investigation and validation[179]. In 2016, the

423 FDA-NIH Biomarker Working Group proposed the development of the BEST (Biomarkers, EndpointS, and

424 other Tools) resource[180]. The BEST resource is a glossary that aims to distinguish between biomarkers and

425 clinical assessments and to describe the distinct functions of biomarkers in biomedical research, clinical

426 practice, and medical product development. BEST can be used to test, validate, and commercialize a

427 biomarker to be used in clinical drug testing trials, and might also be used for improving biomarker

428 development for early OA.

429 The profiling of biological fluids (for example, serum and synovial fluid) and joint tissues can provide a

430 global view of the physiologic state of an OA joint. Refinements in omics approaches and advances in

431 analytical techniques will enable improved profiling of different stages of disease. To be clinically useful

432 these biomarkers need to be properly qualified (that is, a process needs to link a biomarker with other

433 biological, biomechanical and clinical outcomes) for early OA and they must adhere to the BEST guidelines

434 to be effectively used in a clinical setting, rather than in an exploratory and research setting.

435 Soluble biomarkers require further study, validation, and qualification as susceptibility or risk outcomes

436 for the development of early OA before being adopted for widespread use in the clinical care setting. Their

437 contextualized evaluation in all OA research studies is encouraged.

438

439 **Conclusions**

440 Various outcome domains exist that could be assessed for patients with early knee OA in research and/or

441 clinical settings, including patient-reported outcomes, clinical features, measures of physical function,

442 adiposity, physical activity or nutrition and biomechanical, imaging, or biochemical markers. Promising

443 patient reported outcomes for this purpose include the KOOS and the ICOAP. Measures of physical

444 outcomes (for example, single leg hop, quadriceps strength) and fat mass index (DXA) are also valid and

445 reliable. With increasing popularity worldwide, a validated wearable physical activity monitor for

446 quantifying levels of physical activity and a 3-day weighed food record for nutritional intake (for example,

447 calories) has potential. MRI-defined OA and biomarkers, although promising, require specific healthcare

448 and research settings where these outcomes are possible to collect. Additional considerations of patient-

449 preferences and psychosocial outcomes are also important in future research examining early knee OA

450 outcome measures[181]. In this regard, further patient-engaged research is recommended.

451 Importantly, multiple factors must be considered to facilitate risk assessment and the development of

452 predictive models for early knee OA. Furthermore, definitions are needed for the potential outcomes,

453 exposures, confounding and effect-modifying variables, duration of the clinically relevant prediction

454 period and the setting in which the risk prediction tool will be used. As such, further research validating

455 outcomes in individuals 'at risk' of early OA progression (for example, individuals with an intra-articular

456 knee injury and/or who are obese) and 'early-OA' populations is required.

457 **REFERENCES**

458 1. Suri P, Morgenroth DC, Hunter DJ. Epidemiology of osteoarthritis and associated comorbidities.
459 *PM&R*.4,5,S10-S9 (2012)
460 2. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years
461 (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global
462 Burden of Disease Study 2010. *The Lancet*.380,9859,2197-223 (2013)
463 3. Bombardier C, Hawker G, Mosher D. The impact of arthritis in Canada: today and over the next 30
464 years. Arthritis Alliance of Canada 2011:
465 4. Wright EA, Katz JN, Cisternas MG, Kessler CL, Wagenseller A, Losina E. Impact of knee osteoarthritis on
466 health care resource utilization in a US population-based national sample. *Med Care*.48,9,785-91 (2010)
467 5. Losina E, Walensky RP, Reichmann WM, Holt HL, Gerlovin H, Solomon DH, et al. Impact of obesity and
468 knee osteoarthritis on morbidity and mortality in older Americans. *Annals of Internal
469 Medicine*.154,4,217-26 (2011)
470 6. Whittaker JL, Toomey CM, Woodhouse LJ, Jaremko JL, Nettel-Aguirre A, Emery CA. Association
471 between MRI-defined osteoarthritis, pain, function and strength 3–10 years following knee joint injury in
472 youth sport. *Br J Sports Med*.bjsports-2017-097576 (2017)
473 7. World Health Organization Collaborating Centre for Metabolic Bone Diseases. FRAX WHO Fracture Risk
474 Assessment Tool UK: University of Sheffield; 2011 [cited 2015 16/11/2015].
475 https://www.shef.ac.uk/FRAX/tool.jsp].
476 8. Hippisley-Cox J, Coupland C. Derivation and validation of updated QFracture algorithm to predict risk
477 of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study.
478 *BMJ*.344,e3427 (2012)
479 9. Viswanathan M, Reddy S, Berkman N, Cullen K, Middleton J, Nicholson W, et al. Screening to Prevent
480 Osteoporotic Fractures: Updated Evidence Report and Systematic Review for the US Preventive Services
481 Task Force. *JAMA*.319,24,2532-51 (2018)
482 10. Kerkhof H, Bierma-Zeinstra S, Arden N, Metrustry S, Castano-Betancourt M, Hart D, et al. Prediction
483 model for knee osteoarthritis incidence, including clinical, genetic and biochemical risk factors. *Annals of
484 the Rheumatic Diseases*.73,12,2116-21 (2014)
485 11. Roemer FW, Kwoh CK, Hayashi D, Felson DT, Guermazi A. The role of radiography and MRI for
486 eligibility assessment in DMOAD trials of knee OA. *Nature Reviews Rheumatology*.14,6,372-80 (2018)
487 12. Luyten F, Bierma-Zeinstra S, Dell'Accio F, Kraus V, Nakata K, Sekiya I, et al. Toward classification
488 criteria for early osteoarthritis of the knee. *Seminars in Arthritis and Rheumatism*.47,4,457-63 (2017)
489 13. Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: International Knee
490 Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis
491 Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form
492 (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale,
493 Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC),
494 Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care & Research*.63,S11,S208-S28
495 (2011)

496 14. Collins N, Prinsen C, Christensen R, Bartels E, Terwee C, Roos E. Knee Injury and Osteoarthritis
497 Outcome Score (KOOS): systematic review and meta-analysis of measurement properties. *Osteoarthritis*
498 *and Cartilage*.24,6,1317-29 (2016)
499 15. Broderick JE, Schneider S, Junghaenel DU, Schwartz JE, Stone AA. Validity and reliability of patient-
500 reported outcomes measurement information system instruments in osteoarthritis. *Arthritis care &*
501 *research*.65,10,1625-33 (2013)
502 16. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual analog scale for pain (vas
503 pain), numeric rating scale for pain (nrs pain), mcgill pain questionnaire (mpq), short-form mcgill pain
504 questionnaire (sf-mpq), chronic pain grade scale (cpgs), short form-36 bodily pain scale (sf-36 bps), and
505 measure of intermittent and constant osteoarthritis pain (icoap). *Arthritis Care & Research*.63,S11,S240-
506 S52 (2011)
507 17. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome
508 measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*.113,1,9-19 (2005)
509 18. Gooberman-Hill R, Woolhead G, MacKichan F, Ayis S, Williams S, Dieppe P. Assessing chronic joint
510 pain: lessons from a focus group study. *Arthritis Care & Research*.57,4,666-71 (2007)
511 19. Hawker G, Stewart L, French M, Cibere J, Jordan J, March L, et al. Understanding the pain experience
512 in hip and knee osteoarthritis–an OARSI/OMERACT initiative. *Osteoarthritis and Cartilage*.16,4,415-22
513 (2008)
514 20. Maly MR, Cott CA. Being careful: a grounded theory of emergent chronic knee problems. *Arthritis*
515 *Care & Research*.61,7,937-43 (2009)
516 21. Hensor E, Dube B, Kingsbury SR, Tennant A, Conaghan PG. Toward a Clinical Definition of Early
517 Osteoarthritis: Onset of Patient-Reported Knee Pain Begins on Stairs. Data From the Osteoarthritis
518 Initiative. *Arthritis Care & Research*.67,1,40-7 (2015)
519 22. Hawker G, Davis A, French M, Cibere J, Jordan J, March L, et al. Development and preliminary
520 psychometric testing of a new OA pain measure–an OARSI/OMERACT initiative. *Osteoarthritis and*
521 *Cartilage*.16,4,409-14 (2008)
522 23. Gignac MA, Cott C, Badley EM. Adaptation to disability: applying selective optimization with
523 compensation to the behaviors of older adults with osteoarthritis. *Psychology and Aging*.17,3,520-4
524 (2002)
525 24. Morden A, Jinks C, Ong BN. Lay models of self-management: how do people manage knee
526 osteoarthritis in context? *Chronic Illness*.7,3,185–200 (2011)
527 25. Clark JM, Chesworth BM, Speechley M, Petrella RJ, Maly MR. Questionnaire to Identify Knee
528 Symptoms: Development of a Tool to Identify Early Experiences Consistent With Knee Osteoarthritis.
529 *Physical Therapy*.94,1,111-20 (2014)
530 26. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome
531 Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther*.28,2,88-
532 96 (1998)
533 27. Örtqvist M, Roos EM, Broström EW, Janarv P-M, Iversen MD. Development of the knee injury and
534 osteoarthritis outcome score for children (KOOS-Child) comprehensibility and content validity. *Acta*
535 *Orthopaedica*.83,6,666-73 (2012)
536 28. Roos EM, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS)-validation and
537 comparison to the WOMAC in total knee replacement. *Health Qual Life Outcomes*.1,1,17 (2003)
538 29. Roos EM, Roos H, Ekdahl C, Lohmander L. Knee injury and Osteoarthritis Outcome Score (KOOS)-
539 validation of a Swedish version. *Scandinavian Journal of Medicine & Science in Sports*.8,6,439-48 (1998)
540 30. Paradowski PT, Bergman S, Sundén-Lundius A, Lohmander LS, Roos EM. Knee complaints vary with
541 age and gender in the adult population. Population-based reference data for the Knee injury and
542 Osteoarthritis Outcome Score (KOOS). *BMC Musculoskeletal Disorders*.7,1,38 (2006)
543 31. Williamson T, Sikka R, Tompkins M, Nelson BJ. Use of the Knee Injury and Osteoarthritis Outcome
544 Score in a Healthy United States Population. *Am J Sports Med*.44,2,440-6 (2015)

545 32. NIH. NIMH Data Archive: The Osteoarthritis Initiative: National Institute of Health/USA.gov; [cited
546 2019]. This data repository provides access to the data and images from the eleven year OAI longitudinal
547 cohort study.]. Available from: https://nda.nih.gov/oai.
548 33. Bastick A, Wesseling J, Damen J, Verkleij S, Emans P, Bindels P, et al. Defining knee pain trajectories in
549 early symptomatic knee osteoarthritis in primary care: 5-year results from a nationwide prospective
550 cohort study (CHECK). *The British journal of general practice : the journal of the Royal College of General
551 Practitioners*.66,642,e32-9 (2016)
552 34. Wesseling J, Dekker J, Van den Berg W, Bierma-Zeinstra S, Boers M, Cats H, et al. CHECK (Cohort Hip
553 and Cohort Knee): similarities and differences with the Osteoarthritis Initiative. *Annals of the Rheumatic
554 Diseases*.68,9,1413-9 (2009)
555 35. Kastelein M. **Traumatic and Non-traumatic Knee Complaints in General Practice**: *Erasmus MC:
556 University Medical Center Rotterdam*; 2013. 978-94-6191640-2
557 36. Schiphof D, Waarsing E, Oei E, Bierma-Zeinstra S. Crepitus, joint line tenderness and the feeling of
558 giving way are predictive signs for early knee osteoarthritis. *Osteoarthritis and Cartilage*.23,A330 (2015)
559 37. Schiphof D, van Middelkoop M, de Klerk BM, Oei EH, Hofman A, Koes BW, et al. Crepitus is a first
560 indication of patellofemoral osteoarthritis (and not of tibiofemoral osteoarthritis). *Osteoarthritis
561 Cartilage*.22,5,631-8 (2014)
562 38. Maricar N, Callaghan MJ, Parkes MJ, Felson DT, O'Neill TW. Interobserver and Intraobserver
563 Reliability of Clinical Assessments in Knee Osteoarthritis. *J Rheumatol*.43,12,2171-8 (2016)
564 39. Andriacchi TP, Mundermann A, Smith RL, Alexander EJ, Dyrby CO, Koo S. A framework for the in vivo
565 pathomechanics of osteoarthritis at the knee. *Annals of Biomedical Engineering*.32,3,447-57 (2004)
566 40. World Health Organization. International classification of functioning, disability and health: ICF.
567 Geneva, Switzerland: World Health Organization; 2001.
568 41. Dobson F, Hinman R, Hall M, Terwee C, Roos EM, Bennell K. Measurement properties of
569 performance-based measures to assess physical function in hip and knee osteoarthritis: a systematic
570 review. *Osteoarthritis and Cartilage*.20,12,1548-62 (2012)
571 42. Dobson F, Hinman R, Roos EM, Abbott J, Stratford P, Davis A, et al. OARSI recommended
572 performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis.
573 *Osteoarthritis and Cartilage*.21,8,1042-52 (2013)
574 43. Kroman SL, Roos EM, Bennell KL, Hinman RS, Dobson F. Measurement properties of performance-
575 based outcome measures to assess physical function in young and middle-aged people known to be at
576 high risk of hip and/or knee osteoarthritis: a systematic review. *Osteoarthritis and Cartilage*.22,1,26-39
577 (2014)
578 44. Whittaker J, Woodhouse L, Nettel-Aguirre A, Emery C. Outcomes associated with early post-
579 traumatic osteoarthritis and other negative health consequences 3–10 years following knee joint injury
580 in youth sport. *Osteoarthritis and Cartilage*.23,7,1122-9 (2015)
581 45. Baltich J, Whittaker J, Von Tscharner V, Nettel-Aguirre A, Nigg BM, Emery C. The impact of previous
582 knee injury on force plate and field-based measures of balance. *Clinical Biomechanics*.30,8,832-8 (2015)
583 46. Whittaker J, Toomey CM, Nettel-Aguirre A, Jaremko JL, Doyle-Baker PK, Woodhouse LJ, et al. Health-
584 related Outcomes following a Youth Sport-related Knee Injury. *Med Sci Sports Exerc*.epub ahead of print
585 (2018)
586 47. Moksnes H, Engebretsen L, Eitzen I, Risberg MA. Functional outcomes following a non-operative
587 treatment algorithm for anterior cruciate ligament injuries in skeletally immature children 12 years and
588 younger. A prospective cohort with 2 years follow-up. *Br J Sports Med*.47,8,488-94 (2013)
589 48. Moksnes H, Risberg MA. Performance-based functional evaluation of non-operative and operative
590 treatment after anterior cruciate ligament injury. *Scandinavian Journal of Medicine & Science in
591 Sports*.19,3,345-55 (2009)

592 49. Grindem H, Eitzen I, Moksnes H, Snyder-Mackler L, Risberg MA. A Pair-Matched Comparison of
593 Return to Pivoting Sports at 1 Year in Anterior Cruciate Ligament-Injured Patients After a Nonoperative
594 Versus an Operative Treatment Course. *Am J Sports Med*.40,11,2509-16 (2012)
595 50. Logerstedt D, Grindem H, Lynch A, Eitzen I, Engebretsen L, Risberg MA, et al. Single-Legged Hop Tests
596 as Predictors of Self-Reported Knee Function After Anterior Cruciate Ligament Reconstruction The
597 Delaware-Oslo ACL Cohort Study. *Am J Sports Med*.40,10,2348-56 (2012)
598 51. Gribble PA, Hertel J, Plisky P. Using the Star Excursion Balance Test to assess dynamic postural-
599 control deficits and outcomes in lower extremity injury: a literature and systematic review. *Journal of*
600 *Athletic Training*.47,3,339-57 (2012)
601 52. Plisky PJ, Rauh MJ, Kaminski TW, Underwood FB. Star Excursion Balance Test as a predictor of lower
602 extremity injury in high school basketball players. *Journal of Orthopaedic & Sports Physical*
603 *Therapy*.36,12,911-9 (2006)
604 53. Herrington L, Hatcher J, Hatcher A, McNicholas M. A comparison of Star Excursion Balance Test reach
605 distances between ACL deficient patients and asymptomatic controls. *The Knee*.16,2,149-52 (2009)
606 54. Shaffer SW, Teyhen DS, Lorenson CL, Warren RL, Koreerat CM, Straseske CA, et al. Y-balance test: a
607 reliability study involving multiple raters. *Military Medicine*.178,11,1264-70 (2013)
608 55. Hegedus EJ, McDonough SM, Bleakley C, Baxter D, Cook CE. Clinician-friendly lower extremity
609 physical performance tests in athletes: a systematic review of measurement properties and correlation
610 with injury. Part 2—the tests for the hip, thigh, foot and ankle including the star excursion balance test.
611 *Br J Sports Med*.49,10,649-56 (2015)
612 56. Jones CJ, Rikli RE. Measuring functional. *The Journal on Active Aging*.1,24-30 (2002)
613 57. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in
614 community-residing older adults. *Research Quarterly for Exercise and Sport*.70,2,113-9 (1999)
615 58. Rikli RE, Jones CJ. Functional fitness normative scores for community-residing older adults, ages 60-
616 94. *Journal of Aging and Physical Activity*.7,162-81 (1999)
617 59. Ekegren CL, Miller WC, Celebrini RG, Eng JJ, Macintyre DL. Reliability and validity of observational risk
618 screening in evaluating dynamic knee valgus. *Journal of Orthopaedic & Sports Physical Therapy*.39,9,665-
619 74 (2009)
620 60. Weeks BK, Carty CP, Horan SA. Kinematic predictors of single-leg squat performance: a comparison of
621 experienced physiotherapists and student physiotherapists. *BMC Musculoskeletal Disorders*.13,1,207
622 (2012)
623 61. Crossley KM, Zhang W-J, Schache AG, Bryant A, Cowan SM. Performance on the single-leg squat task
624 indicates hip abductor muscle function. *Am J Sports Med*.39,4,866-73 (2011)
625 62. Lorenzen K, Zandiyeh P, Whittaker J, Küpper J, Ronsky J, Emery C. Kinetics and kinematics of the knee
626 during a single leg squat 3-10 years after AN intra-articular knee injury sustained while participating in
627 youth sports. *Osteoarthritis and Cartilage*.23,A104 (2015)
628 63. Emery CA, Cassidy JD, Klassen TP, Rosychuk RJ, Rowe BH. Development of a clinical static and
629 dynamic standing balance measurement tool appropriate for use in adolescents. *Physical*
630 *Therapy*.85,6,502-14 (2005)
631 64. Aandstad A, Holme I, Berntsen S, Anderssen SA. Validity and reliability of the 20 meter shuttle run
632 test in military personnel. *Military Medicine*.176,5,513-8 (2011)
633 65. Øiestad BE, Juhl CB, Eitzen I, Thorlund JB. Knee extensor muscle weakness is a risk factor for
634 development of knee osteoarthritis. A systematic review and meta-analysis. *Osteoarthritis and*
635 *Cartilage*.23,2,171-7 (2015)
636 66. Wang X, Hunter D, Xu J, Ding C. Metabolic triggered inflammation in osteoarthritis. *Osteoarthritis and*
637 *Cartilage*.23,1,22-30 (2015)
638 67. Chu CR, Williams AA, Coyle CH, Bowers ME. Early diagnosis to enable early treatment of pre-
639 osteoarthritis. *Arthritis Research & Therapy*.14,3,212 (2012)

640 68. Richmond SA, Fukuchi RK, Ezzat A, Schneider K, Schneider G, Emery CA. Are joint injury, sport activity,
641 physical activity, obesity, or occupational activities predictors for osteoarthritis? A systematic review. *J*
642 *Orthop Sports Phys Ther*.43,8,515-B19 (2013)
643 69. Mezhov V, Ciccutini F, Hanna F, Brennan S, Wang Y, Urquhart D, et al. Does obesity affect knee
644 cartilage? A systematic review of magnetic resonance imaging data. *Obesity Reviews*.15,2,143-57 (2014)
645 70. Lim YZ, Wang Y, Wluka AE, Davies-Tuck ML, Hanna F, Urquhart DM, et al. Association of obesity and
646 systemic factors with bone marrow lesions at the knee: a systematic review. *Seminars in Arthritis and*
647 *Rheumatism*.43,5,600-12 (2014)
648 71. Lohmander LS, de Verdier MG, Rollof J, Nilsson PM, Engström G. Incidence of severe knee and hip
649 osteoarthritis in relation to different measures of body mass: a population-based prospective cohort
650 study. *Annals of the Rheumatic Diseases*.68,4,490-6 (2009)
651 72. Visser AW, Ioan-Facsinay A, de Mutsert R, Widya RL, Loef M, de Roos A, et al. Adiposity and hand
652 osteoarthritis: the Netherlands Epidemiology of Obesity study. *Arthritis Research & Therapy*.16,1,R19
653 (2014)
654 73. Teichtahl AJ, Wang Y, Wluka AE, Szramka M, English DR, Giles GG, et al. The longitudinal relationship
655 between body composition and patella cartilage in healthy adults. *Obesity*.16,2,421-7 (2008)
656 74. Cibere J, Zhang H, Thorne A, Wong H, Singer J, Kopec JA, et al. Association of clinical findings with
657 pre–radiographic and radiographic knee osteoarthritis in a population-based study. *Arthritis Care &*
658 *Research*.62,12,1691-8 (2010)
659 75. Berry P, Wluka A, Davies-Tuck M, Wang Y, Strauss B, Dixon J, et al. The relationship between body
660 composition and structural changes at the knee. *Rheumatology*.49,12,2362-9 (2010)
661 76. Visser A, de Mutsert R, Loef M, le Cessie S, den Heijer M, Bloem J, et al. The role of fat mass and
662 skeletal muscle mass in knee osteoarthritis is different for men and women: the NEO study.
663 *Osteoarthritis and Cartilage*.22,2,197-202 (2014)
664 77. Ding C, Stannus O, Cicuttini F, Antony B, Jones G. Body fat is associated with increased and lean mass
665 with decreased knee cartilage loss in older adults: a prospective cohort study. *International Journal of*
666 *Obesity*.37,6,822-7 (2013)
667 78. Wang Y, Wluka AE, English DR, Teichtahl AJ, Giles GG, O'Sullivan R, et al. Body composition and knee
668 cartilage properties in healthy, community-based adults. *Annals of the Rheumatic Diseases*.66,9,1244-8
669 (2007)
670 79. Myer GD, Faigenbaum AD, Foss KB, Xu Y, Khoury J, Dolan LM, et al. Injury initiates unfavourable
671 weight gain and obesity markers in youth. *Br J Sports Med*.bjsports-2012-091988 (2013)
672 80. Onat A, Uğur M, Can G, Yüksel H, Hergenç G. Visceral adipose tissue and body fat mass: predictive
673 values for and role of gender in cardiometabolic risk among Turks. *Nutrition*.26,4,382-9 (2010)
674 81. Toomey CM, Whittaker J, Nettel-Aguirre A, reimer RA, Woodhouse LJ, Ghali B, et al. Higher Fat Mass
675 Is Associated With a History of Knee Injury in Youth Sport. *Journal of Orthopaedic & Sports Physical*
676 *Therapy*.47,2,80-7 (2017)
677 82. Miller ME, Rejeski WJ, Reboussin BA, Have TR, Ettinger WH. Physical activity, functional limitations,
678 and disability in older adults. *Journal of the American Geriatrics Society*.48,10,1264-72 (2000)
679 83. Vignon É, Valat J-P, Rossignol M, Avouac B, Rozenberg S, Thoumie P, et al. Osteoarthritis of the knee
680 and hip and activity: a systematic international review and synthesis (OASIS). *Joint Bone Spine*.73,4,442-
681 55 (2006)
682 84. Chmelo E, Nicklas B, Davis C, Miller GD, Legault C, Messier S. Physical activity and physical function in
683 older adults with knee osteoarthritis. *Journal of Physical Activity & Health*.10,6,777-83 (2013)
684 85. Rejeski WJ, Ettinger WH, Jr., Martin K, Morgan T. Treating disability in knee osteoarthritis with
685 exercise therapy: a central role for self-efficacy and pain. *Arthritis Care Res*.11,2,94-101 (1998)
686 86. Hovis KK, Stehling C, Souza RB, Haughom BD, Baum T, Nevitt M, et al. Physical activity is associated
687 with magnetic resonance imaging–based knee cartilage T2 measurements in asymptomatic subjects with
688 and those without osteoarthritis risk factors. *Arthritis & Rheumatism*.63,8,2248-56 (2011)

24

689 87. Lin W, Alizai H, Joseph GB, Srikhum W, Nevitt MC, Lynch JA, et al. Physical activity in relation to knee
690 cartilage T2 progression measured with 3 T MRI over a period of 4 years: data from the Osteoarthritis
691 Initiative. *Osteoarthritis And Cartilage / OARS, Osteoarthritis Research Society*.21,10,1558-66 (2013)
692 88. Dunlop DD, Song J, Semanik PA, Sharma L, Bathon JM, Eaton CB, et al. Relation of physical activity
693 time to incident disability in community dwelling adults with or at risk of knee arthritis: prospective
694 cohort study. *BMJ*.348,g2472 (2014)
695 89. Santos-Lozano A, Santín-Medeiros F, Cardon G, Torres-Luque G, Bailón R, Bergmeir C, et al. Actigraph
696 GT3X: validation and determination of physical activity intensity cut points. *Int J Sports Med*.34,11,975-
697 82 (2013)
698 90. Strath SJ, Kaminsky LA, Ainsworth BE, Ekelund U, Freedson PS, Gary RA, et al. Guide to the
699 assessment of physical activity: Clinical and research applications: a scientific statement from the
700 American Heart Association. *Circulation*.128,20,2259-79 (2013)
701 91. Butte NF, Ekelund U, Westerterp KR. Assessing Physical Activity Using Wearable Monitors: Measures
702 of Physical Activity. *Medicine and Science in Sports and Exercise*.44,1 Suppl 1,S5-S12 (2012)
703 92. Ahn GE, Song J, Lee J, Semanik PA, Chang RW, Sharma L, et al. **Relationship of Objective to Self-**
704 **Reported Physical Activity Measures Among Adults in the Osteoarthritis Initiative.** Abstract. Arthritis
705 and Rheumatism 2012. 64. p. S104-S5
706 93. Christensen R, Astrup A, Bliddal H. Weight loss: the treatment of choice for knee osteoarthritis? A
707 randomized trial. *Osteoarthritis and Cartilage*.13,1,20-7 (2005)
708 94. Bartels E, Christensen R, Christensen P, Henriksen M, Bennett A, Gudbergsen H, et al. Effect of a 16
709 weeks weight loss program on osteoarthritis biomarkers in obese patients with knee osteoarthritis: a
710 prospective cohort study. *Osteoarthritis and Cartilage*.22,11,1817-25 (2014)
711 95. Zheng H, Chen C. Body mass index and risk of knee osteoarthritis: systematic review and meta-
712 analysis of prospective studies. *BMJ Open*.5,12,e007568 (2015)
713 96. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed
714 with knee osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis*.66,4,433-9 (2007)
715 97. Dai Z, Niu J, Zhang Y, Jacques P, Felson DT. Dietary intake of fibre and risk of knee osteoarthritis in
716 two US prospective cohorts. *Ann Rheum Dis*.76,8,1411-9 (2017)
717 98. Ameye LG, Chee WS. Osteoarthritis and nutrition. From nutraceuticals to functional foods: a
718 systematic review of the scientific evidence. *Arthritis Research & Therapy*.8,4,R127 (2006)
719 99. Sanghi D, Mishra A, Sharma AC, Raj S, Mishra R, Kumari R, et al. Elucidation of Dietary Risk Factors in
720 Osteoarthritis Knee—A Case-Control Study. *Journal of the American College of Nutrition*.34,1,15-20
721 (2015)
722 100. Subar AF, Kirkpatrick SI, Mittl B, Zimmerman TP, Thompson FE, Bingley C, et al. The Automated Self-
723 Administered 24-hour dietary recall (ASA24): a resource for researchers, clinicians, and educators from
724 the National Cancer Institute. *J Acad Nutr Diet*.112,8,1134-7 (2012)
725 101. Schröder H, MEstruch, RMartínez-González, MA Corella, D Salas-Salvadó, J Lamuela-Raventós, R
726 Ros, E Salaverría, IFiol, M Lapetra, J Vinyoles, E Gómez-Gracia, E Lahoz, C Serra-Majem, L Pintó, XRuiz-
727 Gutierrez, VCovas, MI. A short screener is valid for assessing Mediterranean diet adherence among older
728 Spanish men and women. *J Nutr*.141,6,1140-5 (2011)
729 102. Sturnieks DL, Besier TF, Mills PM, Ackland TR, Maguire KF, Stachowiak GW, et al. Knee joint
730 biomechanics following arthroscopic partial meniscectomy. *Journal of Orthopaedic Research*.26,8,1075-
731 80 (2008)
732 103. Gardinier ES, Manal K, Buchanan TS, Snyder-Mackler L. Altered loading in the injured knee after ACL
733 rupture. *Journal of Orthopaedic Research*.31,3,458-64 (2013)
734 104. Haughom BD, Souza R, Schairer WW, Li X, Ma CB. Evaluating rotational kinematics of the knee in
735 ACL-ruptured and healthy patients using 3.0 Tesla magnetic resonance imaging. *Knee Surgery, Sports
736 Traumatology, Arthroscopy*.20,4,663-70 (2012)

25

737 105. Waite J, Beard D, Dodd C, Murray D, Gill H. In vivo kinematics of the ACL-deficient limb during
738 running and cutting. *Knee Surgery, Sports Traumatology, Arthroscopy.*13,5,377-84 (2005)
739 106. Zhang L-Q, Shiavi RG, Limbird TJ, Minorik JM. Six degrees-of-freedom kinematics of ACL deficient
740 knees during locomotion—compensatory mechanism. *Gait & posture.*17,1,34-42 (2003)
741 107. Noyes FR, Schipplein OD, Andriacchi TP, Saddemi SR, Weise M. The anterior cruciate ligament-
742 deficient knee with varus alignment An analysis of gait adaptations and dynamic joint loadings. *Am J*
743 *Sports Med.*20,6,707-16 (1992)
744 108. Hubley-Kozey C, Deluzio K, Landry S, McNutt J, Stanish W. Neuromuscular alterations during walking
745 in persons with moderate knee osteoarthritis. *Journal of Electromyography and Kinesiology.*16,4,365-78
746 (2006)
747 109. Heiden TL, Lloyd DG, Ackland TR. Knee joint kinematics, kinetics and muscle co-contraction in knee
748 osteoarthritis patient gait. *Clinical Biomechanics.*24,10,833-41 (2009)
749 110. Mündermann A, Dyrby CO, Andriacchi TP. Secondary gait changes in patients with medial
750 compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking. *Arthritis &*
751 *Rheumatism.*52,9,2835-44 (2005)
752 111. Rudolph KS, Schmitt LC, Lewek MD. Age-related changes in strength, joint laxity, and walking
753 patterns: are they related to knee osteoarthritis? *Physical Therapy.*87,11,1422-32 (2007)
754 112. Hortobágyi T, Westerkamp L, Beam S, Moody J, Garry J, Holbert D, et al. Altered hamstring-
755 quadriceps muscle balance in patients with knee osteoarthritis. *Clinical Biomechanics.*20,1,97-104 (2005)
756 113. Benedetti M, Catani F, Bilotta T, Marcacci M, Mariani E, Giannini S. Muscle activation pattern and
757 gait biomechanics after total knee replacement. *Clinical Biomechanics.*18,9,871-6 (2003)
758 114. Kuntze G, von Tscharner V, Hutchison C, Ronsky JL. Alterations in lower limb multimuscle activation
759 patterns during stair climbing in female total knee arthroplasty patients. *Journal of*
760 *Neurophysiology.*114,5,2718-25 (2015)
761 115. Kuntze G, von Tscharner V, Hutchison C, Ronsky J. Multi-muscle activation strategies during walking
762 in female post-operative total joint replacement patients. *Journal of Electromyography and*
763 *Kinesiology.*25,4,715-21 (2015)
764 116. Cicuttini F, Wluka A, Hankin J, Wang Y. Longitudinal study of the relationship between knee angle
765 and tibiofemoral cartilage volume in subjects with knee osteoarthritis. *Rheumatology.*43,3,321-4 (2004)
766 117. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease
767 progression and functional decline in knee osteoarthritis. *JAMA.*286,2,188-95 (2001)
768 118. Wikstrom EA, Tillman MD, Chmielewski TL, Borsa PA. Measurement and evaluation of dynamic joint
769 stability of the knee and ankle after injury. *Sports Medicine.*36,5,393-410 (2006)
770 119. Riemann BL, Lephart SM. The sensorimotor system, part II: the role of proprioception in motor
771 control and functional joint stability. *Journal of Athletic Training.*37,1,80-4 (2002)
772 120. Williams GN, Buchanan TS, Barrance PJ, Axe MJ, Snyder-Mackler L. Quadriceps weakness, atrophy,
773 and activation failure in predicted noncopers after anterior cruciate ligament injury. *Am J Sports*
774 *Med.*33,3,402-7 (2005)
775 121. Suter E, Herzog W. Does Muscle Inhibition after Knee Injury Increase the Risk of Osteoarthritis?
776 *Exercise and Sport Sciences Reviews.*28,1,15-8 (2000)
777 122. Hurley MV. The role of muscle weakness in the pathogenesis of osteoarthritis. *Rheumatic Disease*
778 *Clinics of North America.*25,2,283-98 (1999)
779 123. Bennell KL, Hunt MA, Wrigley TV, Lim B-W, Hinman RS. Role of muscle in the genesis and
780 management of knee osteoarthritis. *Rheumatic Disease Clinics of North America.*34,3,731-54 (2008)
781 124. Roos EM, Herzog W, Block JA, Bennell KL. Muscle weakness, afferent sensory dysfunction and
782 exercise in knee osteoarthritis. *Nature Reviews Rheumatology.*7,1,57-63 (2011)
783 125. Van de Velde SK, Bingham JT, Hosseini A, Kozanek M, DeFrate LE, Gill TJ, et al. Increased
784 tibiofemoral cartilage contact deformation in patients with anterior cruciate ligament deficiency.
785 *Arthritis & Rheumatism.*60,12,3693-702 (2009)

786 126. Liu F, Kozanek M, Hosseini A, Van de Velde SK, Gill TJ, Rubash HE, et al. In vivo tibiofemoral cartilage
787 deformation during the stance phase of gait. *Journal of Biomechanics*.43,4,658-65 (2010)
788 127. Gardinier ES, Di Stasi S, Manal K, Buchanan TS, Snyder-Mackler L. Knee contact force asymmetries in
789 patients who failed return-to-sport readiness criteria 6 months after anterior cruciate ligament
790 reconstruction. *Am J Sports Med*.42,12,2917-25 (2014)
791 128. Gardinier ES, Manal K, Buchanan TS, Snyder-Mackler L. Clinically-relevant measures associated with
792 altered contact forces in patients with anterior cruciate ligament deficiency. *Clinical*
793 *Biomechanics*.29,5,531-6 (2014)
794 129. Andriacchi TP, Favre J, Erhart-Hledik J, Chu CR. A systems view of risk factors for knee osteoarthritis
795 reveals insights into the pathogenesis of the disease. *Annals of Biomedical Engineering*.43,2,376-87
796 (2015)
797 130. Gardiner BS, Woodhouse FG, Besier TF, Grodzinsky AJ, Lloyd DG, Zhang L, et al. Predicting Knee
798 Osteoarthritis. *Annals of Biomedical Engineering*.1-12 (2015)
799 131. Kobsar D, Osis ST, Phinyomark A, Boyd JE, Ferber R. Reliability of gait analysis using wearable
800 sensors in patients with knee osteoarthritis. *Journal of Biomechanics*.49,16,3977-82 (2016)
801 132. Kobsar D, Osis ST, Boyd JE, Hettinga BA, Ferber R. Wearable sensors to predict improvement
802 following an exercise intervention in patients with knee osteoarthritis. *Journal of Neuroengineering and*
803 *Rehabilitation*.14,1,94 (2017)
804 133. Tadano S, Takeda R, Sasaki K, Fujisawa T, Tohyama H. Gait characterization for osteoarthritis
805 patients using wearable gait sensors (H-Gait systems). *Journal of Biomechanics*.49,5,684-90 (2016)
806 134. Sutter EG, Widmyer MR, Utturkar GM, Spritzer CE, Garrett WE, Jr., DeFrate LE. In vivo measurement
807 of localized tibiofemoral cartilage strains in response to dynamic activity. *Am J Sports Med*.43,2,370-6
808 (2015)
809 135. Chehab EF, Favre J, Erhart-Hledik JC, Andriacchi TP. Baseline knee adduction and flexion moments
810 during walking are both associated with 5 year cartilage changes in patients with medial knee
811 osteoarthritis. *Osteoarthritis and Cartilage*.22,11,1833-9 (2014)
812 136. Walter JP, Kinney AL, Banks SA, D'Lima DD, Besier TF, Lloyd DG, et al. Muscle synergies may improve
813 optimization prediction of knee contact forces during walking. *Journal of Biomechanical*
814 *Engineering*.136,2,021031 (2014)
815 137. Gerus P, Sartori M, Besier TF, Fregly BJ, Delp SL, Banks SA, et al. Subject-specific knee joint geometry
816 improves predictions of medial tibiofemoral contact forces. *Journal of Biomechanics*.46,16,2778-86
817 (2013)
818 138. Johnson WR, Alderson J, Lloyd DG, Mian A. Predicting Athlete Ground Reaction Forces and
819 Moments from Spatio-temporal Driven CNN Models. *IEEE Transactions on Biomedical Engineering*.Early
820 Access (2018)
821 139. Long MJ, Papi E, Duffell LD, McGregor AH. Predicting knee osteoarthritis risk in injured populations.
822 *Clinical biomechanics*.47,87-95 (2017)
823 140. Pfeiffer S, Harkey M, Stanley L, Blackburn J, Padua D, Spang J, et al. Associations Between Slower
824 Walking Speed and T1ρ Magnetic Resonance Imaging of Femoral Cartilage Following Anterior Cruciate
825 Ligament Reconstruction. *Arthritis Care Res*.70,8,1132-40 (2018)
826 141. Chu CR, Sheth S, Erhart-Hledik J, Do B, Titchenal M, Andriacchi T. Mechanically stimulated
827 biomarkers signal cartilage changes over 5 years consistent with disease progression in medial knee
828 osteoarthritis patients. *J Orthop Res*.36,3,891-7 (2018)
829 142. Pietrosimone B, Loeser R, Blackburn J, Padua D, Harkey M, Stanley L, et al. Biochemical markers of
830 cartilage metabolism are associated with walking biomechanics 6-months following anterior cruciate
831 ligament reconstruction. *J Orthop Res*.35,10,2288-97 (2017)
832 143. Favre J, Erhart-Hledik J, Chehab E, Andriacchi T. Baseline ambulatory knee kinematics are associated
833 with changes in cartilage thickness in osteoarthritic patients over 5 years. *J Biomech*.49,9,1859-64 (2016)

27

834 144. Erhart-Hledik J, Favre J, Asay J, Smith R, Giori N, Mündermann A, et al. A relationship between
835 mechanically-induced changes in serum cartilage oligomeric matrix protein (COMP) and changes in
836 cartilage thickness after 5 years. *Osteoarthritis Cartilage*.20,11,1309-15 (2012)
837 145. Brandt KD, Fife RS, Braunstein EM, Katz B. Radiographic grading of the severity of knee
838 osteoarthritis: relation of the Kellgren and Lawrence grade to a grade based on joint space narrowing,
839 and correlation with arthroscopic evidence of articular cartilage degeneration. *Arthritis &
840 Rheumatism*.34,11,1381-6 (1991)
841 146. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Annals of the Rheumatic
842 Diseases*.16,4,494-502 (1957)
843 147. Wirth W, Duryea J, Hellio Le Graverand MP, John MR, Nevitt M, Buck RJ, et al. Direct comparison of
844 fixed flexion, radiography and MRI in knee osteoarthritis: responsiveness data from the Osteoarthritis
845 Initiative. *Osteoarthritis Cartilage*.21,1,117-25 (2013)
846 148. Hunter DJ, Guermazi A, Lo GH, Grainger AJ, Conaghan PG, Boudreau RM, et al. Evolution of semi-
847 quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). *Osteoarthritis
848 and Cartilage*.19,8,990-1002 (2011)
849 149. Guermazi A, Niu JB, Hayashi D, Roemer FW, Englund M, Neogi T, et al. Prevalence of abnormalities
850 in knees detected by MRI in adults without knee osteoarthritis: population based observational study
851 (Framingham Osteoarthritis Study). *British Medical Journal*.345,e5339 (2012)
852 150. Sharma L, Guermazi A, Almagor O, Crema M, Dunlop DD, Roemer F, et al. **T**issue Lesions in
853 Osteoarthritis Initiative Participants with Normal X-Rays and Risk Factors for Incident Cartilage Damage.
854 Abstract. Arthritis and Rheumatism Annual Scientific Meeting of the American College of Rheumatology
855 and Association of Rheumatology Health Professionals; Washington, DC, United States: John Wiley and
856 Sons Inc. ; 2012. S1039-S40
857 151. Su F, Hilton JF, Nardo L, Wu S, Liang F, Link TM, et al. Cartilage morphology and T 1 and T 2
858 quantification in ACL-reconstructed knees: a 2-year follow-up. *Osteoarthritis and Cartilage*.21,8,1058-67
859 (2013)
860 152. Van Ginckel A, Verdonk P, Witvrouw E. Cartilage adaptation after anterior cruciate ligament injury
861 and reconstruction: implications for clinical management and research? A systematic review of
862 longitudinal MRI studies. *Osteoarthritis and Cartilage*.21,8,1009-24 (2013)
863 153. Hunter DJ, Lohmander LS, Makovey J, Tamez-Peña J, Totterman S, Schreyer E, et al. The effect of
864 anterior cruciate ligament injury on bone curvature: exploratory analysis in the KANON trial.
865 *Osteoarthritis and cartilage*.22,7,959-68 (2014)
866 154. Neogi T, Felson DT. Osteoarthritis: Bone as an imaging biomarker and treatment target in OA.
867 *Nature Reviews Rheumatology*.12,9,503-4 (2016)
868 155. Bowes M, Lohmander L, Wolstenholme C, Vincent G, Conaghan P, Frobell R. Marked and rapid
869 change of bone shape in acutely ACL injured knees–an exploratory analysis of the Kanon trial.
870 *Osteoarthritis and cartilage*. (2019)
871 156. Hunter DJ, Arden N, Conaghan PG, Eckstein F, Gold G, Grainger A, et al. Definition of osteoarthritis
872 on MRI: results of a Delphi exercise. *Osteoarthritis and Cartilage*.19,8,963-9 (2011)
873 157. Schiphof D, Oei E, Hofman A, Waarsing J, Weinans H, Bierma-Zeinstra S. Sensitivity and associations
874 with pain and body weight of an MRI definition of knee osteoarthritis compared with radiographic
875 Kellgren and Lawrence criteria: a population-based study in middle-aged females. *Osteoarthritis and
876 Cartilage*.22,3,440-6 (2014)
877 158. Culvenor AG, Collins NJ, Guermazi A, Cook JL, Vicenzino B, Khan KM, et al. Early knee osteoarthritis
878 is evident one year following anterior cruciate ligament reconstruction: a magnetic resonance imaging
879 evaluation. *Arthritis & Rheumatology*.67,4,946-55 (2015)
880 159. Hunter D, Altman R, Cicuttini F, Crema M, Duryea J, Eckstein F, et al. OARSI Clinical Trials
881 Recommendations: Knee imaging in clinical trials in osteoarthritis. *Osteoarthritis and Cartilage*.23,5,698-
882 715 (2015)

883 160. Roemer FW, Frobell R, Lohmander LS, Niu J, Guermazi A. Anterior Cruciate Ligament OsteoArthritis
884 Score (ACLOAS): longitudinal MRI-based whole joint assessment of anterior cruciate ligament injury.
885 *Osteoarthritis and cartilage*.22,5,668-82 (2014)
886 161. Guermazi A, Roemer FW, Hayashi D, Crema MD, Niu J, Zhang Y, et al. Assessment of synovitis with
887 contrast-enhanced MRI using a whole-joint semiquantitative scoring system in people with, or at high
888 risk of, knee osteoarthritis: the MOST study. *Annals of the Rheumatic Diseases*.70,5,805-11 (2011)
889 162. Magnusson K, Kumm J, Turkiewicz A, Englund M. A naturally aging knee, or development of early
890 knee osteoarthritis? *Osteoarthritis and cartilage*.26,11,1447-52 (2018)
891 163. Baert IA, Staes F, Truijen S, Mahmoudian A, Noppe N, Vanderschueren G, et al. Weak associations
892 between structural changes on MRI and symptoms, function and muscle strength in relation to knee
893 osteoarthritis. *Knee Surgery, Sports Traumatology, Arthroscopy*.22,9,2013-25 (2014)
894 164. Neogi T, Felson D, Niu J, Nevitt M, Lewis CE, Aliabadi P, et al. Association between radiographic
895 features of knee osteoarthritis and pain: results from two cohort studies. *Bmj*.339,b2844 (2009)
896 165. Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS. Call for standardized definitions of
897 osteoarthritis and risk stratification for clinical trials and clinical use. *Osteoarthritis and
898 Cartilage*.23,8,1233-41 (2015)
899 166. Bruyère O, Genant H, Kothari M, Zaim S, White D, Peterfy C, et al. Longitudinal study of magnetic
900 resonance imaging and standard X-rays to assess disease progression in osteoarthritis. *Osteoarthritis and
901 Cartilage*.15,1,98-103 (2007)
902 167. Hayashi D, Felson D, Niu J, Hunter D, Roemer F, Aliabadi P, et al. Pre-radiographic osteoarthritic
903 changes are highly prevalent in the medial patella and medial posterior femur in older persons:
904 Framingham OA study. *Osteoarthritis and Cartilage*.22,1,76-83 (2014)
905 168. Englund M, Guermazi A, Gale D, Hunter DJ, Aliabadi P, Clancy M, et al. Incidental meniscal findings
906 on knee MRI in middle-aged and elderly persons. *New England Journal of Medicine*.359,11,1108-15
907 (2008)
908 169. Felson D, Lohmander L. Whither osteoarthritis biomarkers? *Osteoarthritis and cartilage/OARS,
909 Osteoarthritis Research Society*.17,4,419 (2009)
910 170. Bay-Jensen AC, Thudium CS, Mobasheri A. Development and use of biochemical markers in
911 osteoarthritis: current update. *Current Opinion in Rheumatology*.30,1,121-8 (2017)
912 171. Ling SM, Patel DD, Garnero P, Zhan M, Vaduganathan M, Muller D, et al. Serum protein signatures
913 detect early radiographic osteoarthritis. *Osteoarthritis and Cartilage*.17,1,43-8 (2009)
914 172. Golightly YM, Marshall SW, Kraus VB, Renner JB, Villaveces A, Casteel C, et al. 124 Serum Cartilage
915 Oligomeric Matrix Protein Hyaluronan High-Sensitivity C-Reactive Protein and Keratan Sulfate as
916 Predictors of Incident Radiographic Knee Osteoarthritis: Differences by Chronic Knee Symptoms.
917 *Osteoarthritis and Cartilage*.18,S62-S3 (2010)
918 173. Blumenfeld O, Williams FM, Hart DJ, Spector TD, Arden N, Livshits G. Association between cartilage
919 and bone biomarkers and incidence of radiographic knee osteoarthritis (RKOA) in UK females: a
920 prospective study. *Osteoarthritis Cartilage*.21,7,923-9 (2013)
921 174. Sowers M, Lachance L, Jamadar D, Hochberg MC, Hollis B, Crutchfield M, et al. The associations of
922 bone mineral density and bone turnover markers with osteoarthritis of the hand and knee in pre- and
923 perimenopausal women. *Arthritis Rheum*.42,3,483-9 (1999)
924 175. Kosinska MK, Liebisch G, Lochnit G, Wilhelm J, Klein H, Kaesser U, et al. Sphingolipids in Human
925 Synovial Fluid: A Lipidomic Study. *PLOS One*.9,3,e91769 (2014)
926 176. Adams S, Setton LA, Kensicki E, Bolognesi MP, Toth AP, Nettles DL. Global metabolic profiling of
927 human osteoarthritic synovium. *Osteoarthritis and Cartilage*.20,1,64-7 (2012)
928 177. Bauer D, Hunter D, Abramson S, Attur M, Corr M, Felson D, et al. Classification of osteoarthritis
929 biomarkers: a proposed approach. *Osteoarthritis and Cartilage*.14,8,723-7 (2006)

930   178. Kraus VB, Blanco F, Englund M, Henrotin Y, Lohmander L, Losina E, et al. OARSI Clinical Trials
931   Recommendations: Soluble biomarker assessments in clinical trials in osteoarthritis. *Osteoarthritis and*
932   *cartilage*.23,5,686-97 (2015)
933   179. Van Spil W, DeGroot J, Lems W, Oostveen J, Lafeber F. Serum and urinary biochemical markers for
934   knee and hip-osteoarthritis: a systematic review applying the consensus BIPED criteria. *Osteoarthritis*
935   *and cartilage*.18,5,605-12 (2010)
936   180. (FDA) SSMUFaDA. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet] 2016.
937   Available from: https://www.ncbi.nlm.nih.gov/books/NBK326791/?report=reader
938   181. van der Elst K, Meyfroidt S, De Cock D, De Groef A, Binnard E, Moons P, et al. Unraveling Patient-
939   Preferred Health and Treatment Outcomes in Early Rheumatoid Arthritis: A Longitudinal Qualitative
940   Study. *Arthritis Care Res (Hoboken)*.68,9,1278-87 (2016)

941

948

949   **Author contributions**

950   "CAE, JLW, NKA, AMa, LSL, EMR, KLB, CMT, RAR, DT, JLR, GK, DGL, TA, ME, VBK, EL, SBZ, JR, GP, FPL, LSM,

951   MAR, AMo, AG, DJH, NKA researched data for the article. CAE, JLW, NKA, AMa, LSL, EMR, KLB, CMT, RAR,

952   DT, JLR, GK, DGL, TA, ME, VBK, EL, SBZ, JR, GP, FPL, LSM, MAR, AMo, AG, DJH, NKA provided substantial

953   contributions to discussion of content. CAE, JLW, NKA, AMa, LSL, and FPL wrote the article and CAE, JLW,

954   NKA, AMa, LSL, EMR, KLB, CMT, RAR, DT, JLR, GK, DGL, TA, ME, VBK, EL, SBZ, JR, GP, FPL, LSM, MAR, AMo,

955   AG, DJH, NKA reviewed and/or edited the manuscript before submission."

956   **Competing Interests**

957   CAE, JLW, AMa, NKA, KLB, CMT, RAR, DT, JLR, GK, DGL, TA, ME, VBK, EL, SBZ, JR, GP, FPL, LSM, MAR, AMo,

961

962 <u>Related links</u>

963 KOOS scoring instructions: http://www.koos.nu/

964 Single Leg Hop for distance: https://www.sralab.org/rehabilitation-measures/single-limb-hop-tests

965 30-second Chair Sit-to-Stand Test: https://vimeo.com/74649743

966 6-minute walk test: https://vimeo.com/74649737

Box 1. Proposed outcomes for the assessment of early pre-radiographic OA

Below we provide suggestions for outcomes measures that could be used to assess individuals with early pre-radiographic OA in clinical practice and in research settings. Further research is needed, including evaluation of validity of early-OA specific outcomes and change in outcomes with progression of OA as many of these measures have been evaluated primarily in established OA.

In clinical practice and research settings:

Patient-reported outcomes

The Knee Injury and Osteoarthritis Outcome Score (KOOS) can be used to measure pain during activity, other symptoms (e.g., stiffness, grinding, catching, swelling, knee flexion and extension) , function in daily life and during sport and recreational activities, and quality of life across different age and treatment groups. The intermittent and constant assessment of pain score (ICOAP) can evaluate constant and intermittent pain.

Clinical examination

A clinical assessment including joint line tenderness should be performed on individuals with newly-onset symptoms of knee pain, stiffness, crepitus, or a feeling of 'giving way'.

Functional outcomes

Three measures seem promising for use in clinical settings on the basis of their reproducibility, patient acceptability and the equipment and expertise required: Single leg hop test, 30 second chair sit-to-stand and quadriceps strength measure. Multiple additional functional measures have been validated for use in research settings.

Lifestyle-related outcomes

Adiposity can be assessed by body fat percentage or fat mass index (fat mass/height^2) using dual-energy x-ray absorptiometry or bioelectrical impedance analysis if available. BMI is more feasible in clinical settings, although has limitations for use in athletes. Levels of physical activity can be assessed using a validated physical activity monitor or a validated questionnaire if objective methods are not available. Nutrition outcomes are not currently suggested for use in routine clinical care, however the 3-day dietary record provides reliable estimates of nutrient intake.

In research settings only:

Biomechanical outcomes

Measures of biomechanical outcomes require further research and are not currently suggested for use in routine clinical care. However, such outcomes are ideal for informing the underlying mechanisms of OA progression and informing treatment interventions in research setting.

Imaging outcomes

The utility of plain radiography in early OA is limited. Although MRI has superior sensitivity to change and validity in the context of early OA, and is hence ideal in research settings, MRI is not thought appropriate for the routine clinical care setting because of the high cost and potential risk of over-diagnosis.

Biomarkers

No biomarkers are currently of use in routine clinical care; however, further validation of proteomic, lipidomic and metabolomic tools in research settings could lead to informative cartilage and synovial fluid profiles and provide important insights into OA progression.

Commented [CE1]: Thought of others on this addition?

967

968

969
970
971

972
973
974

975 **Table 1. I**mportant physical function outcomes
976

Outcome measure	Test measure	Equipment Required	Reliability			Error	Validity		Responsive /Interpreta bility	Appropriate risk group (age)	References
			Intra	Inter	Re-test		Struct-ural	Ho testing			
Single leg hop for distance	Length (cm)	Measuring tape	+	-	-	-	-	+/-	-	Post-trauma (≤45 years)	43, 44, 47-50
Cross hop for distance	Length (cm)	Measuring tape	+	-	-	-	-	+/-	-	Post-trauma (≤45 years)	40,44-4
6 meter timed hop test	Time (sec)	Measuring tape	+	-	-	-	-	+	-	Post-trauma (≤45 years)	43, 47-50
Star excursion balance test	Length (% leg length)	Measuring mat, measuring tape and skilled rater (leg length)	+	+	+	+	-	+/-	-	Post-trauma or obese (all ages)	44, 51-55
30-second chair sit-to-stand test	Count	Chair and timer	+	+	-	-	-	-	-	Post-trauma or obese (all ages)	53-55
6 minute walk test	Length (m)	Flat 20m walking area, timer and chair	-	-	-	-	-	-	-	Obese (all ages)	41, 42
Vertical drop jump	Risk rating	31cm high box	+	+	-	-	-	+/-	-	Post-trauma (≤45 years)	44, 59
Single leg squat	Risk rating	None	+	+	-	-	+/-	+/-	-	Post-trauma or obese (all ages)	44, 60-62
Unipedal dynamic balance	Time (sec)	Balance pad and timer	-	+	+	-	+	+	-	Post-trauma or obese (all ages)	41,61
20 meter shuttle run	Stage	Coloured tape and instructions.	-	-	+	+	-/+	+	-	Post-trauma (≤45 years)	41,61
Quadriceps strength	Force (Nm/Kg)	Hand-held or isokinetic dynamometer and skilled rater	+	+	+	+	+	+	+	Post-trauma or obese (all ages)	44, 47, 48, 51, 65
Hamstring strength	Force (Nm/Kg)	Hand-held or isokinetic dynamometer and skilled rater	+	+	+	+	+/-	+/-	+/-	Post-trauma or obese (all ages)	41,43

34

| Hip adductor or hip abductor strength | Force (Nm/Kg) | Hand-held or isokinetic dynamometer and skilled rater | + | + | + | + | - | +/- | - | Post-trauma or obese (all ages) | 41,43 | 977 978 |

983 + = supporting evidence, - = no supporting evidence, +/- = conflicting evidence,

986
987

Box 2 MRI-defined osteoarthritis[92]

Tibio-femoral MRI-defined osteoarthritis (OA) is based on identifying the following MRI features in the medial or lateral tibio-femoral compartment:

- Definite osteophyte AND full thickness cartilage loss

Or

- Definite osteophyte OR full thickness cartilage loss AND at least two of the following:
  - Sub-chondral bone marrow lesion not associated with meniscal or ligamentous attachment.
  - Meniscal subluxation (for example, meniscal extrusion), maceration or degeneration (including horizontal tear).
  - Partial thickness cartilage loss where full-thickness loss was not present.
  - Bone attrition in one of the tibiofemoral (medial or lateral) or patellofemoral joint compartments respectively.

Mixed Tibio-femoral MRI-defined OA is based on meeting some of the above features in one compartment and others in a second compartment.

Patellofemoral MRI-defined OA is based on identifying a definite osteophyte and partial or full-thickness cartilage loss in the patellofemoral compartment

---

988

989

990

991

992

993

994

995

996

997