EULAR EVIDENCE BASED RECOMMENDATIONS FOR THE DIAGNOSIS OF KNEE OSTEOARTHRITIS


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ABSTRACT

Objectives: To develop evidence based recommendations for the diagnosis of knee osteoarthritis (OA).

Methods: The multidisciplinary guideline development group, representing 12 European countries, generated 10 key propositions regarding diagnosis using a Delphi consensus approach. For each recommendation research evidence was searched systematically. Whenever possible, the sensitivity, specificity and likelihood ratio were calculated for individual diagnostic indicators and a diagnostic ladder was developed using Bayes’ method. Secondary analyses were undertaken to directly test the recommendations using multiple predictive models in two populations from the UK and the Netherlands. Strength of recommendation was assessed by the EULAR visual analogue scale.

Results: Recommendations covered the definition of knee OA and its risk factors, subsets, typical symptoms and signs, the use of imaging and laboratory tests, and differential diagnosis. Three symptoms (persistent knee pain, limited morning stiffness and reduced function) and three signs (crepitus, restricted movement and bony enlargement) appeared to be the most useful. Assuming a 12.5% background prevalence of knee OA in adults aged 45 years and older, the estimated probability of having radiographic knee OA increased with increasing number of positive features, to 99% when all 6 symptoms and signs were present. The performance of the recommendations in the study populations varied according to the definition of knee OA, background risk and number of tests applied.

Conclusion: 10 key recommendations for diagnosis of knee OA were developed using both research evidence and expert consensus. Although there is no agreed reference standard, thorough clinical assessment alone can provide a confident rule-in diagnosis.

Key words: EULAR recommendations, knee osteoarthritis, diagnosis
INTRODUCTION

Osteoarthritis (OA) is the third most common diagnosis made by general practitioners in older patients\(^1\), and OA is the most common arthropathy to affect the knee\(^2,3\). About 25% of adults aged over 55 years experience significant knee pain; half of these have radiographic changes of OA and a quarter have significant disability.\(^4\) Risk factors for knee OA include ageing\(^5\), female gender\(^6\), being overweight\(^7\), prior knee injury\(^8\) and a positive family history\(^9\). However, knee OA is not a discrete entity, showing variability with respect to compartmental involvement, accompanying inflammation and calcium crystal deposition, concurrence of OA at other joint sites\(^10\), and outcome.

Classification criteria developed by the American College of Rheumatology (ACR) in 1986 are often used to standardise case definitions for research purposes\(^11\). Currently there is no guideline primarily for the purpose of clinical diagnosis of knee OA. Radiography is often used as a “gold” standard, but it is not the only marker for OA. Definition of knee OA may change according to different levels of care and clinical requirements. Therefore the EULAR OA Task Force undertook the following project to develop evidence-based recommendations for diagnosis of knee OA using a systematic review of research evidence and expert consensus\(^12\). Performance of the recommendations was tested in two European populations. The target audience for these recommendations is any health professional who is involved with the diagnosis of knee OA.

METHODS

A multidisciplinary guideline development group, comprising 17 OA experts from 12 European countries, was commissioned by the EULAR Standing Committee for Clinical Affairs (ESCCA). Following a single face-to-face meeting, each participant independently submitted up to 10 propositions related to key aspects in diagnosis of knee OA. Consensus was reached using the Delphi technique\(^13\). As with previous EULAR projects to develop recommendations for diagnosis\(^14,15\), a systematic search of the literature published between January 1950 and January 2008 was undertaken; the search for knee OA was combined with searches for diagnostic test and study design (Appendices 1-7, available from www.ard.org). Further search for specific diagnostic test/feature was undertaken after consensus to ratify the evidence.

Outcome measures

As there is no agreed single reference standard for the diagnosis of knee OA, a pragmatic decision was made to include studies that included either clinical, radiographic, magnetic resonance imaging (MRI) or arthroscopic reference standards. The ability of individual tests to discriminate between patients with and without knee OA was then summarised by sensitivity, specificity, and likelihood ratios (LR) (LR = sensitivity / (1-specificity))\(^16,17\). LRs above 10 or below 0.1 are considered strong evidence to respectively rule in or rule out a diagnosis in most circumstances\(^17\). The probability of having knee OA given a positive test result was estimated using Bayes’ theorem\(^17\). Test reliability was
summarised using kappa statistics (dichotomous data) and intra-class correlation coefficients (continuous data). Relative risk (RR) and odds ratio (OR) were calculated for risk factors and co-morbidities associated with knee OA\textsuperscript{18}. For economic evaluations, the incremental cost-effective ratio (ICER) was presented\textsuperscript{19}. Best available evidence was used according to the EULAR evidence hierarchy for diagnosis (I\textsubscript{a} = meta-analysis of cohort studies; I\textsubscript{b} = meta-analysis of case control or cross sectional studies; II\textsubscript{a} = cohort studies; II\textsubscript{b} = case control or cross sectional studies; III = non-comparative descriptive studies; IV = expert opinion)\textsuperscript{14}. Statistical pooling was undertaken as appropriate within the same study design if there was no systematic review and random effects model was used when the results were heterogenous\textsuperscript{20}. Strength of recommendation (SOR) was graded using the EULAR 0-100 mm visual analogue scale (VAS)\textsuperscript{21}. The performance of the recommended tests was examined in two populations\textsuperscript{22,23}, where multiple logistic regression was used to estimate the likelihood of knee OA given a composite of the diagnostic tests\textsuperscript{24}. All measures were reported with 95\% confidence interval (CI) unless otherwise specified.

**Future research agenda**

After the propositions for diagnosis had been searched, reviewed and discussed, each participant submitted independently 10 propositions for future research. Consensus was again obtained using the Delphi technique.

**RESULTS**

**Systematic literature search**

The literature search yielded 1738 hits. After deleting duplications, 1604 studies remained, of which 313 met the inclusion criteria (Figure 1). Clinical features (36\%) and radiographs were the most often used reference standards (35\%). The majority of studies were cross-sectional (55\%), followed by case control (29\%), cohort (13\%) and systematic review (3\%). No randomised controlled trials or economic evaluations were identified from the search.

**EULAR recommendations**

Of 166 propositions suggested initially, 10 were agreed after 4 anonymous Delphi rounds. Recommendations covered the definition of knee OA and its risk factors, subsets, typical symptoms and signs, the use of imaging and laboratory tests, and differential diagnosis (Table 1). Evidence regarding validity (sensitivity, specificity etc) and reliability of each diagnostic test/feature were summarised in Table 2. Three symptoms (persistent knee pain, limited morning stiffness and reduced function) and three signs (crepitus, restricted movement and bony enlargement) appeared to be the most useful. Assuming a 12.5\% background prevalence of knee OA in adults aged 45 years and older, the estimated probability of having radiographic knee OA increased with increasing number of positive features, to 99\% when all 6 symptoms and signs were present. Strength of recommendation was generated based on research evidence and clinical expertise with 95\% confidence interval (Table 1). Details of each recommendation and supporting evidence are available online in EULAR
Table 1. Propositions and strength of recommendation (SOR) – order according to topic (definition, subsets, symptoms, physical findings, images, laboratory tests, risk factors and differential diagnosis)

<table>
<thead>
<tr>
<th>No</th>
<th>Proposition</th>
<th>LoE</th>
<th>SOR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Knee OA is characterised clinically by usage-related pain and/or functional limitation. It is a common complex joint disorder showing focal cartilage loss, new bone formation and involvement of all joint tissues. Structural tissue changes are mirrored in classical radiographic features.</td>
<td>IIb</td>
<td>88 (83-92)</td>
</tr>
<tr>
<td>2</td>
<td>Risk factors that are strongly associated with the incidence of knee OA can help identify patients in whom knee OA is the most likely diagnosis. These include increasing age over 50 years, female gender, higher body mass index, previous knee injury or malalignment, joint laxity, occupational or recreational usage, family history and the presence of Heberden’s nodes.</td>
<td>Ia-IIb</td>
<td>89 (83-95)</td>
</tr>
<tr>
<td>3</td>
<td>Subsets with different risk factors and outcomes can be defined according to: varying compartmental involvement (patellofemoral, medial tibiofemoral, lateral tibiofemoral); bone response (atrophic, hypertrophic); the global pattern of OA (generalised, localised); by crystal presence (pyrophosphate, basic calcium phosphates); and by the degree of inflammation. However, the ability to discriminate subsets and the relevance for routine practice are unclear.</td>
<td>Ib-IIb</td>
<td>75 (63-87)</td>
</tr>
<tr>
<td>4</td>
<td>Typical symptoms of knee OA are usage-related pain, often worse towards the end of the day, relieved by rest; the feeling of “giving way”; only mild morning or inactivity stiffness; and impaired function. More persistent rest and night pain may occur in advanced OA. OA symptoms are often episodic or variable in severity and slow to change.</td>
<td>Ib-IIb</td>
<td>76 (64-87)</td>
</tr>
<tr>
<td>5</td>
<td>In adults aged &gt;40 years with usage-related knee pain, only short-lived morning stiffness, functional limitation and one or more typical examination findings (crepitus, restricted movement, bony enlargement) a confident diagnosis of knee OA can be made without a radiographic examination. This applies even if radiographs appear normal.</td>
<td>Ib</td>
<td>80 (67-92)</td>
</tr>
<tr>
<td>6</td>
<td>All patients with knee pain should be examined. Findings indicative of knee OA include: crepitus; painful and/or restricted movement; bony enlargement; and absent or modest effusion. Additional features that may be present include: deformity (fixed flexion and/or varus - less commonly valgus); instability; periarticular or joint-line tenderness; and pain on patellofemoral compression.</td>
<td>Ia-III</td>
<td>90 (85-95)</td>
</tr>
<tr>
<td>7</td>
<td>Red flags (eg severe local inflammation, erythema, progressive pain unrelated to usage) suggest sepsis, crystals or serious bone pathology. Involvement of other joints may suggest a wide range of alternative diagnoses. Other important considerations are referred pain, ligamentous and meniscal lesions and localised bursitis.</td>
<td>IV</td>
<td>87 (80-94)</td>
</tr>
<tr>
<td>8</td>
<td>Plain radiography (both knees, weight-bearing, semi-flexed PA (MTP) view, plus a lateral and skyline view) is the current “gold” standard for morphological assessment of knee OA. Classical features are focal joint space narrowing, osteophyte, subchondral bone sclerosis and subchondral “cysts”. Further imaging modalities (MRI, sonography, scintigraphy) are seldom indicated for diagnosis of OA</td>
<td>Ib-IIb</td>
<td>83 (71-95)</td>
</tr>
<tr>
<td>9</td>
<td>Laboratory tests on blood, urine or synovial fluid are not required for the diagnosis of knee OA, but may be used to confirm or exclude coexistent inflammatory disease (e.g. pyrophosphate crystal deposition, gout, rheumatoid arthritis) in patients with suggestive symptoms or signs.</td>
<td>Ib</td>
<td>86 (78-94)</td>
</tr>
<tr>
<td>10</td>
<td>If a palpable effusion is present synovial fluid should be aspirated and analysed to exclude inflammatory disease and to identify urate and calcium pyrophosphate crystals. OA synovial fluid is typically non-inflammatory with &lt;2000 leukocytes/mm³; if specifically sought, basic calcium phosphate crystals are often present.</td>
<td>Ib</td>
<td>73 (56-89)</td>
</tr>
</tbody>
</table>

LoE=level of evidence (Ia=meta-analysis of cohort studies, Ib=meta-analysis of case control or cross sectional studies, IIa=cohort study, IIb=case control or cross-sectional studies, III=non-comparative descriptive studies, IV=expert opinion); SOR=strength of recommendation on visual analogue scale (0-100 mm, 0=not recommended at all, 100=fully recommended); CI: confidence interval.
<table>
<thead>
<tr>
<th>Test</th>
<th>No. studies (designs)</th>
<th>No subjects</th>
<th>Mean age (range)</th>
<th>F%</th>
<th>Reference standards</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>LR (95% CI)</th>
<th>ICC/kappa (95% CI) Intra</th>
<th>Inter</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age≥50</td>
<td>1 (cs)</td>
<td>2865</td>
<td>-</td>
<td>54%</td>
<td>Radiographic</td>
<td>0.90</td>
<td>0.23</td>
<td>1.20</td>
<td>-</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>Female</td>
<td>2 (1 cc, 1 cs)</td>
<td>3102</td>
<td>-</td>
<td>55%</td>
<td>Clinical or radiographic</td>
<td>(0.69, 0.83)</td>
<td>0.31</td>
<td>(0.22, 0.40)</td>
<td>(0.94, 1.29)</td>
<td>-</td>
<td>11.25</td>
</tr>
<tr>
<td>Knee pain</td>
<td>7 (1 cc, 6 cs)</td>
<td>5401</td>
<td>62 (40-92)</td>
<td>62%</td>
<td>Clinical, radiographic or MRI</td>
<td>0.58</td>
<td>0.62</td>
<td>1.57</td>
<td>0.84</td>
<td>0.72</td>
<td>11.29-30</td>
</tr>
<tr>
<td>Persistent*</td>
<td>3 (3cs)</td>
<td>1505</td>
<td>(40-79)</td>
<td>100%</td>
<td>Clinical, radiographic</td>
<td>0.53</td>
<td>0.71</td>
<td>1.67</td>
<td></td>
<td></td>
<td>11.26-31</td>
</tr>
<tr>
<td>Usage-related</td>
<td>4 (1cc, 3cs)</td>
<td>3896</td>
<td>72 (50-92)</td>
<td>54%</td>
<td>Clinical, radiographic</td>
<td>0.95</td>
<td>0.19</td>
<td>1.16</td>
<td></td>
<td></td>
<td>11.27</td>
</tr>
<tr>
<td>Functional limitation</td>
<td>5 (3 cc, 2 cs)</td>
<td>1945</td>
<td>64 (50-90)</td>
<td>54%</td>
<td>Clinical or radiographic</td>
<td>0.56</td>
<td>0.63</td>
<td>1.50</td>
<td></td>
<td></td>
<td>11.28-32</td>
</tr>
<tr>
<td>Persistent*</td>
<td>3 (1 cc, 2 cs)</td>
<td>3151</td>
<td>67 (50-92)</td>
<td>79%</td>
<td>Clinical or radiographic</td>
<td>0.88</td>
<td>0.52</td>
<td>1.84</td>
<td>0.90</td>
<td>0.62</td>
<td>11.29-33</td>
</tr>
<tr>
<td>Persistent*</td>
<td>3 (1 cc, 2 cs)</td>
<td>942</td>
<td>65 (50-92)</td>
<td>72%</td>
<td>Clinical or radiographic</td>
<td>0.89</td>
<td>0.60</td>
<td>2.23</td>
<td>0.78</td>
<td>0.23</td>
<td>11.29-34</td>
</tr>
<tr>
<td>Bony enlargement</td>
<td>3 (1 cc, 2 cs)</td>
<td>3108</td>
<td>59 (44-74)</td>
<td>55%</td>
<td>Clinical or radiographic</td>
<td>0.55</td>
<td>0.95</td>
<td>11.81 (4.94, 28.22)</td>
<td>0.91</td>
<td></td>
<td>11.29-35</td>
</tr>
<tr>
<td>Restricted movement</td>
<td>6 (3 cc, 2 cs, 1 sr)</td>
<td>3661</td>
<td>62 (50-90)</td>
<td>54%</td>
<td>Clinical or radiographic</td>
<td>0.17</td>
<td>0.96</td>
<td>4.4</td>
<td>0.73 – 0.79</td>
<td>0.48 – 1.00</td>
<td>11.29-36</td>
</tr>
<tr>
<td>Instability</td>
<td>2 (1 cc, 1 cs)</td>
<td>243</td>
<td>58 (44-82)</td>
<td>72%</td>
<td>Clinical or radiographic</td>
<td>0.43</td>
<td>0.41</td>
<td>0.73</td>
<td></td>
<td></td>
<td>11.29-37</td>
</tr>
<tr>
<td>Palpable effusion</td>
<td>2 (1 cc, 1 cs)</td>
<td>3752</td>
<td>55 (50-90)</td>
<td>55%</td>
<td>Clinical or radiographic</td>
<td>0.26</td>
<td>0.79</td>
<td>1.25</td>
<td></td>
<td></td>
<td>11.30-38</td>
</tr>
<tr>
<td>JSN</td>
<td>8 (4 cc, 4 cs)</td>
<td>2615</td>
<td>55 (25-80)</td>
<td>78%</td>
<td>Clinical, MRI, or arthroscopic</td>
<td>0.44</td>
<td>0.79</td>
<td>2.19</td>
<td>0.66</td>
<td>0.44</td>
<td>11.30-39</td>
</tr>
<tr>
<td>OST</td>
<td>8 (5 cc, 6 cs)</td>
<td>3250</td>
<td>57 (25-80)</td>
<td>74%</td>
<td>Clinical, MRI or arthroscopic</td>
<td>0.51</td>
<td>0.83</td>
<td>3.29</td>
<td>0.71</td>
<td>0.62</td>
<td>11.30-40</td>
</tr>
<tr>
<td>KL</td>
<td>4 (2 cc, 2 cs)</td>
<td>1853</td>
<td>55 (25-85)</td>
<td>87%</td>
<td>Clinical</td>
<td>0.43</td>
<td>0.85</td>
<td>2.62</td>
<td>0.78</td>
<td>0.67</td>
<td>11.30-41</td>
</tr>
<tr>
<td>Instability</td>
<td>5 (3 cc, 2 cs)</td>
<td>788</td>
<td>55 (25-77)</td>
<td>60%</td>
<td>Clinical or arthroscopic</td>
<td>0.33</td>
<td>0.89</td>
<td>2.56</td>
<td>0.00 - 0.86</td>
<td>-0.04 - 0.67</td>
<td>11.30-42</td>
</tr>
<tr>
<td>Cysts</td>
<td>2 (cc)</td>
<td>387</td>
<td>53 (35-77)</td>
<td>63%</td>
<td>Clinical or arthroscopic</td>
<td>0.24 (-0.04, 0.51)</td>
<td>0.93</td>
<td>2.98</td>
<td></td>
<td></td>
<td>11.30-43</td>
</tr>
</tbody>
</table>

Ref: Table 2. Validity and reliability of diagnostic tests in the diagnosis of knee osteoarthritis – pooled results
<table>
<thead>
<tr>
<th>SF CPPD</th>
<th>RF (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (1 cc, 2 cs)</td>
<td>1 (cc)</td>
</tr>
<tr>
<td>3894</td>
<td>237</td>
</tr>
<tr>
<td>67 (34-98)</td>
<td>55</td>
</tr>
<tr>
<td>51%</td>
<td>73%</td>
</tr>
<tr>
<td>Clinical or radiographic</td>
<td>Clinical</td>
</tr>
<tr>
<td>0.56 (0.48, 0.64)</td>
<td>0.05 (0.003, 0.11)</td>
</tr>
<tr>
<td>0.70 (0.64, 0.76)</td>
<td>0.51 (0.40, 0.63)</td>
</tr>
<tr>
<td>1.87 (1.46, 2.40)</td>
<td>0.11 (0.04, 0.30)</td>
</tr>
</tbody>
</table>

CI=confidence interval; LR=likelihood ratio; ICC=intraclass correlation coefficient; JSN=joint space narrowing; OST osteophyte; KL=Kellgren and Lawrence; cc=case control; cs=cross sectional; sr=systematic review
* most day for at least a month
Performance of recommendations

The two populations selected have investigated plain radiographs and clinical features, permitting performance testing for some of the recommendations.

1. In the UK

We used cross-sectional data from the Knee Clinical Assessment Study (CAS(K)) conducted in North Staffordshire UK. After excluding 16 people with a pre-existing diagnosis of inflammatory arthritis, 745 adults with knee pain aged 50 years and over (mean age: 65 years, SD 8.6, range 50-93; 56% female; mean BMI: 29.6 kg/m², 41% obese) were available for analysis.

Of 745, 570 (76%) and 292 (39%) subjects had radiographic OA according to two definitions based on standing postero-anterior, supine lateral and supine skyline views: osteophytosis (broadly equivalent to KL≥1) and JSN (broadly equivalent to KL≥3). Compartmental distribution of knee OA differed according to the definition. With the first definition, the PF was the most commonly affected compartment (38%); with the second, the medial TF was the most commonly affected (38%). The proportions with chondrocalcinosis in the same knee were 8% and 12% respectively.

Age, gender, BMI, morning stiffness (<30 minutes), crepitus, reduced flexion, bony enlargement, fixed flexion deformity, palpable effusion, and intercondylar/intermalleolar gap (a surrogate for varus/valgus malalignment) were entered in the logistic regression models and backward LR was used to select significant variables. Morning stiffness and intercondylar gap were excluded from the model because they were non-significant.

The probability of radiographic knee OA increased with an increasing number of positive tests (Figure 3). The likelihood of having radiographic knee OA (KL≥1) was 88% for a person aged over 60 years, who is overweight and has crepitus, restricted movement and bony enlargement. The likelihood was smaller when the diagnostic criterion was higher (e.g., KL≥3) (Figure 3).

2. In the Netherlands

The Rotterdam study is a population-based, longitudinal cohort study for incidence and risk factors for chronic disabling conditions. Of 10,275 residents in one district of Rotterdam (Ommoord), 7983 agreed to participate (mean age: 70.6 SD: 9.8, range 55 to 106; 61.1% female, mean BMI: 26.3, SD 3.7), 3456 with baseline knee AP x-rays formed the study population for this analysis.

Of 3456 subjects, 1624 (47%) and 129 (3.7%) were classified as having knee OA according to the cut-offs: KL≥1 and KL≥3. Diagnostic variables examined included age, gender, BMI, knee pain in the last 5 years, morning stiffness, functional impairment, family history of OA, radiographic varus malalignment, hand OA (KL≥2), hip OA (KL≥2) and serum C-reactive protein (CRP) <5. Of these, gender, morning stiffness, family history, hip OA and CRP were not significant so were excluded from the logistic regression models. Only 4 clinical features (age, BMI, knee pain and functional limitation) were available to test the performance of the clinical diagnosis. The probability of having any radiographic knee OA (KL≥1) increased gradually with an increasing number of positive tests. It reached 52% when all these clinical features were positive, i.e.,
aged over 60 years of age, being overweight and having knee pain and impaired function.

**Future research agenda**  
One hundred and thirteen initial propositions were submitted by the Task Force members. After 3 anonymous Delphi rounds, 9 of these obtained over 50% votes and went forward as the proposed future research agenda:

1. Development of internationally agreed criteria sets for diagnosis of knee OA for clinical practice, clinical trials and epidemiological studies
2. Development of a scoring system for accurate diagnosis of knee OA based on the sensitivity and specificity of risk factors and symptoms and signs
3. Delineation of the attributable risk factor profile, both for development and progression, for each suggested subset of knee OA.
4. Development of diagnostic criteria for early symptomatic knee OA (e.g. by prospective investigation of people with knee pain who fulfil criteria of knee OA several years later)
5. Investigation of whether individual pain patterns (usage-related, episodic, night pain) have different utility as diagnostic markers of knee OA
6. Determination of clinical, diagnostic and prognostic relevance of MRI changes in knee OA
7. Determination of the utility of ultrasonography in the diagnosis and prognosis of knee OA
8. Assessment of the possible role of biomarkers (including genetic markers) in the early diagnosis, phenotypic characterisation, and prediction of outcome of knee OA
9. Assessment of the accuracy of red flags in identifying serious pathology in patients presenting with knee symptoms

**DISCUSSION**  
Knee OA can variably involve cartilage, bone, synovium and surrounding tissues of the three biomechanically discrete compartments, and may associate with OA at other joints due to shared genetic and constitutional risk exposures. Thus the clinical phenotype is very variable, requiring consideration of several characteristics for accurate diagnosis. Although the ACR criteria are a useful tool for classification of knee OA they were developed using hospital-referred patients and a control group that comprised patients with other arthritis (over 50% had rheumatoid arthritis), thus making them most useful for differentiation of knee OA from inflammatory arthritis rather than for diagnosis of knee OA per se in a routine clinical setting. The focus of the current recommendations, however, was on the risk factors, symptoms, signs and tests that might contribute to a clinical diagnosis. Although there is no “gold standard” for diagnosis of knee OA, an important conclusion was that in adults aged 45 years or older, an adequate history and examination alone may lead to a confident clinical diagnosis of knee OA. This may contrast with the situation in some care settings in which practitioners devote insufficient time to patient enquiry and physical examination and instead place undue emphasis on tests, especially radiographs.
The recommendations were developed systematically and combine both expert opinion (Delphi exercise) and research evidence (systematic review and meta-analysis)\textsuperscript{12,14}. Evidence was derived both from community and hospital based studies to improve generalisability. The recommendations have been examined initially in datasets derived from two general populations in Europe.

According to the recommendations and the supporting evidence the diagnosis of knee OA can be made based on: the background risk (the population prevalence of knee OA); the patient’s risk factors for OA (e.g. age, gender, BMI, occupation); their symptoms (persistent knee pain, brief morning stiffness and functional limitation); and an adequate physical examination (crepitus, restricted movement and bony enlargement). Plain radiographs are the main test to consider, but are an adjunct, rather than a central feature, for the purposes of diagnosis (Figure 4). The more positive results a patient presents the more likely the diagnosis of OA. Knowledge of the background risk (that is, the local source population prevalence of knee OA) is crucial for estimating the likelihood of knee OA. The higher the risk in the source population, the more possible it is to diagnose knee OA based on clinical features.

There are limitations to these recommendations. Firstly, the evidence to support these recommendations were derived largely from literature based on different studies. The LRs (Table 2) are unadjusted and the subsequent probabilities (Figure 2) are for reference only. The application of these recommendations should be based on the individual patient characteristics and the knee OA risk in the source population. Secondly, the LRs pooled from the literature may be affected by many factors such as the number of studies involved, the populations selected (hospital or community), the gold standard used, and the cut-off values selected. For example, the LR for bony enlargement (11.81, 95%CI 4.94, 28.22) was mainly based on a hospital-based case control study where the gold standard was clinical diagnosis of knee OA and the controls predominantly were RA patients\textsuperscript{11}. The validity and reliability of this LR is questionable, compared to those LRs derived from multiple studies including both hospital and community data, such as for persistent knee pain\textsuperscript{28-30} and crepitus\textsuperscript{27,32,34}. Therefore caution must be exercised when interpreting results obtained using this feature. Thirdly, there is no universally applicable reference standard for knee OA, so the recommendations were mainly based on radiographic evidence when clinical features were examined, or on clinical, MRI or arthroscopic evidence when radiographic features were examined. Whether this is an appropriate approach is open to debate. Finally, all propositions relate to people over age 40 which is the target age for common OA. Whether recommendations would differ for less typical patients under this age was not addressed.

In conclusion, 10 key recommendations for the diagnosis of knee OA have been produced based both on expert consensus and a systematic literature review. A confident diagnosis may be made according to three symptoms (knee pain, short-lived morning stiffness and functional limitation) and determination of three signs on examination (crepitus, restricted movement and bony enlargement) without a requirement for imaging. This may be especially useful
for primary care. Nevertheless, plain radiography and occasionally other investigations may be considered for the diagnosis of atypical cases when additional pathology is suspected. These recommendations were examined in two test populations and the level of evidence and summary strength of recommendations were provided to guide their use.
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**Figure legend:**

Figure 1. Study selection

Figure 2. Likelihood ratio and probability of knee OA (reference standard: radiographic KL≥2)

Figure 3. Clinical features and cumulative probability of radiographic knee OA – evidence from the UK population

Figure 4. Major components in the diagnosis of knee osteoarthritis
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1. Knee OA is characterised clinically by usage-related pain and/or functional limitation. It is a common complex joint disorder showing focal cartilage loss, new bone formation and involvement of all joint tissues. Structural tissue changes are mirrored in classical radiographic features.

**Level of evidence: IIb, Strength of recommendation: 88 (95%CI 83-92)**

There is good evidence that multiple risk factors, including heredity, constitutional, biomechanical and environmental, predispose to knee OA, justifying the term “common complex disorder”\(^1\). Although focal loss of hyaline cartilage and osteophyte are the pathological hallmarks of established OA, involvement of all other joint tissues (meniscal fibrocartilage, synovium, capsule, ligaments and muscle) has been documented in MRI studies and in studies of human knee OA pathology\(^2\-5\). The definition of knee OA varies according to the study purpose. Radiographs are relatively insensitive in showing pathological change and although radiographic change, most commonly a global Kellgren and Lawrence (KL) score \(\geq 2\), is often used to define knee OA in epidemiological studies this has limited value in clinical practice, especially in a primary care setting, where pain and disability are the main causes for consultation\(^6\). For the purpose of the EULAR recommendations, the definition of knee OA should at least reflect the three clinical domains associated with OA - pain, disability and structure change - to ensure adequate diagnosis and management of the disease in different health care settings. The level of evidence to support this proposition is IIb.

2. Risk factors that are strongly associated with the incidence of knee OA can help identify patients in whom knee OA is the most likely diagnosis. These include increasing age over 50 years, female gender, higher body mass index, previous knee injury or malalignment, joint laxity, occupational or recreational usage, family history and the presence of Heberden’s nodes.

**Level of evidence: Ia – IIb, Strength of recommendation: 89 (95%CI 83-95)**

Ageing is a major risk factor for knee OA\(^7\-13\). Knee OA is uncommon in people younger than 40 years of age, and the incidence increases gradually until 80 years of age with greater risk in women than men\(^7\). A systematic review of gender difference has confirmed a higher incidence (RR=1.82, 95%CI 1.06, 3.12) and prevalence (RR=1.59, 95%CI 1.33, 1.89) of knee OA in women\(^14\). High Body Mass Index (BMI) is also associated with knee OA with a relative risk ranging from 2 to 8 depending on the study design, the cut-off value of high BMI and the knee compartment involved\(^9\-15\) (Table 3). The effect of elevated BMI may become more significant in people with knee malalignment\(^19\). Varus
(RR=2.06, 95%CI 1.28, 3.23) and valgus malalignment (1.54, 95%CI 0.94, 2.44) are risk factors for the development of knee OA\(^20\). They are also strongly associated with the progression of the disease (Table 3)\(^{20-23}\). Other risk factors include knee laxity\(^24,25\), family history\(^26\), knee injury\(^27\), mechanically demanding occupational activity\(^28\) or high level of physical activity (running 20 miles/week)\(^29\) (Table 3).

In summary, a number of risk factors for knee OA have been identified, the most established being increasing age over 40, female gender and being overweight. They should be considered in the diagnosis of knee OA, at least as part of the background information. The evidence to support this proposition ranges from Ia to IIb (Table 3).

3. **Subsets with different risk factors and outcomes can be defined**
   
   **according to:** varying compartmental involvement (patellofemoral, medial tibiofemoral, lateral tibiofemoral); bone response (atrophic, hypertrophic); the global pattern of OA (generalised, localised); by crystal presence (pyrophosphate, basic calcium phosphates); and by the degree of inflammation. However, the ability to discriminate subsets and the relevance for routine practice are unclear.

**Level of evidence: Ib – IIb, Strength of recommendation: 75 (95%CI 63-87)**

OA may affect different compartments of the knees. The distribution varies according to the population selected, reflecting differences in disease severity, risk factors and associations\(^30-33\). Compartmental distribution tends to be symmetrical in patients with bilateral disease, although tibio-femoral (TF) but not patello-femoral (PF) changes tend to be more severe on the right\(^34\). In one hospital based study a hypertrophic pattern of bone response was seen in 207 (44%) knees, an atrophic pattern in 89 (19%) and a mixed pattern in 174 (37%)\(^31\).

More severe and multi-compartmental radiographic change may be associated with calcium pyrophosphate crystal deposition (CPPD), nodal change, interphalangeal (IP) OA and body mass index (BMI)\(^31,35\). Two community-based case control studies (n=608 and 325 respectively)\(^15,17\) showed that BMI (highest vs lowest tertiles) was more associated with combined TF and PF OA (pooled OR=7.07, 95%CI 4.01, 12.46), than with isolated TF (OR=2.18, 95%CI 1.41, 3.36) or isolated PF OA (OR=2.79, 95%CI1.61, 4.85). More severe and rapid progression of knee OA is reported in those with clinical signs of inflammation\(^36-39\).

Knee OA is associated with other joint OA, including distal IP (OR=1.8, 95%CI 1.1, 3.1), proximal IP (2.4, 95%CI 1.3, 4.4), carpometacarpal (CMC) (2.4, 95%CI 1.5, 4.4) and hip (2.1, 95%CI 1.2, 3.4) OA\(^40\). These data support the concept of “generalized OA” in which some individuals are at increased risk of multiple joint involvement by OA. Classification criteria for generalized versus localized OA have been proposed\(^41\) although it appears that no single cut-off for the number of joints affected is applicable to all age ranges\(^40\). There is clear justification to include assessment of other target joints for OA for the purpose of prognosis and thus management of knee OA.
In brief, there are data to support division of “subsets” of knee OA according to the variables listed (evidence level IIb). Different compartmental involvement may associate with different risk exposures and outcomes (evidence level Ib). Full assessment of different compartments as well as other joints (e.g., nodal change) should prove helpful for both diagnosis and prognosis. However, the ability to discriminate subsets, and whether this would alter management in routine practice, has not been formally tested.

4. Typical symptoms of knee OA are usage-related pain, often worse towards the end of the day, relieved by rest; the feeling of “giving way”; only mild morning or inactivity stiffness; and impaired function. More persistent rest and night pain may occur in advanced OA. OA symptoms are often episodic or variable in severity and slow to change. Level of evidence: Ib - IIb, Strength of recommendation: 76 (95%CI 64-87)

Pain is the major cause of consultation for patients with knee OA. Knee OA pain often shows worsening towards the afternoon and evening. People with severe structural change may experience pain at night and this may be more common among hospital-referred patients. Seven studies (n=5401) have examined the value of knee pain in the diagnosis of knee OA. Of these studies, 5 used radiographs, one clinical diagnosis and one MRI as the gold standard for diagnosis. Pooled data show a sensitivity of 0.58 (95%CI 0.40, 0.77), a specificity of 0.62 (95%CI 0.45, 0.79) and an LR of 1.57 (95%CI 1.26, 1.96). Usage-related pain was examined in 4 studies (n=3896). This was very sensitive (sensitivity=0.95, 95%CI 0.91, 0.99) but not specific (specificity=0.19, 95%CI 0.11, 0.26), resulting in a small LR (LR=1.16, 95%CI 1.15, 1.29). Persistent knee pain (e.g., pain on most days for at least a month) was examined in 3 studies (n=1505). It was not as sensitive (sensitivity=0.53, 95%CI 0.47, 0.58) but was more specific (specificity=0.71, 95%CI 0.62, 0.79) than usage-related pain. The pooled LR was 1.64 (95%CI 1.45, 1.86) (Table 2).

Similar LRs were obtained for self-reported functional impairment (LR=1.50, 95%CI 1.23, 1.84), and short-lasting (<30 minute) morning and inactivity stiffness (LR=1.84, 95%CI 1.49, 2.27) (Table 2).

The probability of having knee OA, given each of these clinical symptoms is less than 20%, based on the estimate of the UK population risk of knee OA of 12.5% in people aged over 45 years old. However, the probability increases to 34% if all three symptoms are present (Figure 2).

In summary, persistent knee pain, only brief morning or inactivity stiffness and self-reported functional impairment appear to be typical symptoms of knee OA (level of evidence Ib). However, they have limited value for the diagnosis of knee OA per se, even if all three are present (IIb). Pain is often worse towards the end of the day and may extend into the night, but these features have not been examined as diagnostic markers.
5. In adults aged >40 years with usage-related knee pain, only short-lived morning stiffness, functional limitation and one or more typical examination findings (crepitus, restricted movement, bony enlargement) a confident diagnosis of knee OA can be made without a radiographic examination. This applies even if radiographs appear normal. **Level of evidence: Ib, Strength of recommendation: 80 (95%CI 67-92)**

Clinical examination findings play a critical role in the diagnosis of knee OA. Eight studies (n=3947) have examined the value of clinical findings of crepitus, restricted movement and bony enlargement in the diagnosis of knee OA. The majority of these studies used radiographic evidence of knee OA as the gold standard. Although crepitus appears very sensitive, restricted movement and bony enlargement are extremely specific for knee OA (Table 2). The LRs are 2.23 (95%CI 1.90, 2.63) for crepitus, 4.4 (95%CI not available) for restricted movement, and 11.81 (95%CI 4.94, 28.22) for bony enlargement (Table 2). Consequently, the probabilities of a patient having knee OA according to these LRs are 24%, 39% and 63% respectively (Figure 2). The probability increases with a composite of multiple tests (Figure 2), reaching 99% when combining these three physical findings with the previous three key symptoms (i.e. persistent knee pain, morning stiffness and functional impairment). This suggests that a clinical diagnosis of knee OA can be made in most people without radiographic examination.

Knee OA shows a strong age relationship, being uncommon before the age of 40 but increasing steadily with age from then onwards. However, because of its high prevalence after age 40, there is no clear cut-off in middle or old age that can be used to assist diagnosis.

In summary, research evidence provides strong support for the clinical diagnosis of knee OA based on the 3 key symptoms (persistent knee pain, morning stiffness and functional impairment) and the 3 typical clinical signs (crepitus, restricted movement and bony enlargement) (evidence level Ib). This composite gives rise to a probability of over 90% in a population with a background risk of knee OA of 12.5%, and is especially useful in primary care. However, the presence of just one sign is not highly predictive.

6. **All patients with knee pain should be examined. Findings indicative of knee OA include: crepitus; painful and/or restricted movement; bony enlargement; and absent or modest effusion. Additional features that may be present include: deformity (fixed flexion and/or varus - less commonly valgus); instability; periarticular or joint-line tenderness; and pain on patellofemoral compression.** **Level of evidence: Ia – III, Strength of recommendation: 90 (95%CI 85-95)**

People with knee pain often are not adequately examined. In one study only 60% of people who consulted their GP for persistent knee pain (pain for most days for at least a month or longer in the past year) underwent any examination of their knees. This may reflect time constraints, insufficient training in
musculoskeletal assessment, or lack of confidence in the usefulness of clinical signs in diagnosis. As discussed in the previous section, the combined presence of 3 typical signs (crepitus, restricted movement and bony enlargement) greatly increases the chance of the diagnosis. In contrast, palpable effusion is less often present in knee OA than in knees with inflammatory arthritis (LR=0.73, 95%CI 0.56, 0.95). Knee instability is inconstant and present to a similar extent in people with knee OA and controls (LR=1.25, 95%CI 0.89, 1.77) (Table 2). Varus and valgus malalignment both associate with knee OA. The risk of having knee OA is more than 2 times greater in someone with malalignment than in someone without (OR=2.29, 95%CI 1.70, 3.09). Varus deformity carries greater risk (OR=3.02, 1.66, 5.49) than valgus (OR=2.20, 95%CI 1.43, 2.78) (Table 3). Research evidence is sparse for other physical findings such as tenderness and pain on PF compression.

In brief, adequate physical assessment is required in patients with knee pain to confirm the diagnosis of knee OA (evidence level III). The presence of restricted movement, bony enlargement, and either varus or valgus malalignment add support to the diagnosis (evidence level Ia). Clinically evident effusion is uncommon in knee OA. This indicates inflammation and requires differentiation from inflammation caused by other arthritis (evidence level Ib).

7. **Red flags (e.g. severe local inflammation, erythema, progressive pain unrelated to usage) suggest sepsis, crystals and serious bone pathology. Involvement of other joints may suggest a wide range of alternative diagnoses. Other important considerations are referred pain, ligamentous and meniscal lesions and localised bursitis.**

**Level of evidence: IV, Strength of recommendation: 87 (95%CI 80-94)**

Clearly the presence of features that are unexplained by knee OA but which are characteristic of other diseases should lead to consideration, and investigation, of other pathologies. This is particularly important in the presence of “red flags” such as “bony pain” and acute synovitis with overlying erythema. To diagnose any regional abnormality it is important to consider the whole patient, to include a screen of the whole musculoskeletal system (and often other systems), and to combine a detailed history with a sufficient physical examination to determine the likely cause of pain and functional impairment. Although these statements are self-evident and underpin the rationale for clinical assessment, there are no research data that specifically examine the justification of a detailed patient assessment to differentiate knee OA from the many other possible causes of pain experienced in or around the knee (evidence level IV). A recent attempt by EULAR and the European Federation of National Associations of Orthopaedics and Traumatology (EFFORT) to develop evidence-based and consensus recommendations for diagnosis and management of patients with acute or recent onset knee swelling failed to identify relevant, sound research evidence and all recommendations were supported primarily by expert opinion (i.e. level IV evidence).
Plain radiography (both knees, weight-bearing, semi-flexed PA (MTP) view, plus a lateral and skyline view) is the current “gold” standard for morphological assessment of knee OA. Classical features are focal joint space narrowing, osteophyte, subchondral bone sclerosis and subchondral “cysts”. Further imaging modalities (MRI, sonography, scintigraphy) are seldom indicated for diagnosis of OA.

**Level of evidence: Ib – IIb, Strength of recommendation: 83 (95%CI 71-95)**

Structural changes on plain radiographs have been used by 35% of studies as the gold standard for the assessment of a diagnostic test. Two cross sectional studies, one based in hospital (n=377) and the other in the community (n=777), found the sensitivity of a weight-bearing PA (MTP) view plus a lateral or skyline view (0.90, 95%CI 0.84, 0.96) to be higher than that of the PA view alone (0.58, 95%CI 0.55, 0.50)\(^3^0\);\(^6^0\). When both the skyline and lateral views were used with the PA view, 98.7% cases of radiographic OA were identified\(^3^0\). Specificity could not be determined as the studies had no normal controls. Another study comparing 15\(^0\), 30\(^0\), 40\(^0\) flexion and fully extended PA views found the 15\(^0\) flexion view to be the most sensitive for demonstrating JSN \(^6^1\).

The validity of radiographic change has been examined in a number of studies in which the clinical diagnosis\(^3^2;\(^4^3;\(^6^2\), MRI (cartilage defect score ≥2 of the 0-4 scale\(^6^3\)) or arthroscopy (cartilage degeneration, yes/no\(^6^4\)) was used as the gold standard. Classical radiographic features such as joint space narrowing (JSN) and osteophyte are moderately sensitive (0.44, 95%CI 0.27, 0.62 and 0.51, 95%CI 0.32, 0.69) and very specific (0.79, 95%CI 0.66, 0.92 and 0.83, 95%CI 0.76, 0.89). LRs were 2.19 (1.58, 3.03) for JSN\(^3^2;\(^4^3;\(^6^2;\(^6^3;\(^6^5;\(^6^6\) and 3.29 (2.41, 4.48) for osteophyte\(^3^2;\(^4^3;\(^6^2;\(^6^3;\(^6^5;\(^6^6;\(^6^7;\(^6^8\). Similar LRs were obtained for the KL score (LR=2.62, 2.10, 3.26)\(^3^3;\(^4^3;\(^6^5;\(^6^8\), subchondral bone sclerosis (LR=2.56, 1.92, 3.42)\(^4^3;\(^6^2;\(^6^5;\(^6^8\) and subchondral cysts (LR=2.98, 95%CI 1.76, 5.03)\(^4^3;\(^6^6;\(^6^9\)(Table 2).

The resultant probabilities of each of these radiographic features ranges from 24-32%, so none alone can lead to the diagnosis of knee OA. However, a composite of JSN, osteophyte, sclerosis and cysts increases the probability from 24% up to 89%.

The value of MRI and ultrasound (US) in the diagnosis of knee OA have yet to be confirmed. A community based case-control study demonstrated that the cartilage defects determined by MRI were sensitive (0.93, 95%CI 0.84, 1.02), but not specific (0.33, 95%CI 0.16, 0.50) for knee OA defined by KL ≥1\(^7^2\). However, abnormal MRI signals may associate with pain, as shown for bone marrow lesions (BML) or “edema” (OR=1.63, 95%CI=1.30, 2.04)\(^7^3;\(^7^7\) and particularly for effusion (OR=9.9, 95%CI 1.13, 149)\(^7^5\). This is supported by two cross-sectional studies where US was used to determine effusion. People with US defined effusion are 3 and a half times more likely to have pain than those without effusion (OR=3.55, 95%CI 1.75-7.20)\(^3^8;\(^3^9\). Bone scintigraphy is a useful predictor of future structure change/progression but is an invasive investigation with no advantages to offer over other imaging modalities with respect to the diagnosis of knee OA \(^7^8;\(^7^9\).
In conclusion, a weight bearing semi-flexed plain radiograph is a well validated imaging technique to determine structural change of knee OA. It has moderate sensitivity and reasonable specificity to detect cartilage loss and osteophyte (evidence level Ib). Multiple radiographic features greatly increase the likelihood of the diagnosis. MRI is more sensitive but less specific (evidence level IIb), but may be more useful in demonstrating features that associate with pain (evidence level Ib). Ultrasound is a simple and accessible technique to demonstrate effusion and synovial thickening (evidence level Ib).

9. Laboratory tests on blood, urine or synovial fluid are not required for the diagnosis of knee OA, but may be used to confirm or exclude coexistent inflammatory disease (e.g. pyrophosphate crystal deposition, gout, rheumatoid arthritis) in patients with suggestive symptoms or signs.

Level of evidence: IIb, Strength of recommendation: 86 (95% CI 78-94)

Rheumatoid factor may be present in patients with knee OA though less commonly and at lower titre than in those with rheumatoid arthritis, and serum C-reactive protein may be mildly elevated in patients with symptomatic knee OA. Additional biomarkers are under investigation in OA but no marker currently has sufficient specificity and sensitivity for clinical use in diagnosis of knee OA. Knee OA may co-exist with deposition of CPPD and basic calcium phosphate crystals. Analysis of synovial fluid aspirated from OA knees often demonstrate CPPD crystals (35%, 95% CI 19% - 50%)\(^1\)\(^2\)\(^3\)\(^1\)\(^2\)\(^3\), especially in severe cases\(^2\)\(^2\)\(^3\)\(^4\)\(^5\) and basic calcium phosphates, often in combination with CPPD. In addition, synovial joints affected by OA predispose to monosodium urate crystal deposition. Knees affected by OA are three time more likely to have gout than those unaffected by OA (OR=3.07, 95% CI 1.05, 8.96). Synovial fluid examination is the gold standard to confirm coexistence of gout and knee OA, and is also the way in which to determine presence of CPPD.

In brief, although laboratory investigations do not assist, and are not essential for, the diagnosis of knee OA, they may become useful for differential diagnosis and to identify coexistent diseases, especially crystal deposition (evidence level IIb).

10. If a palpable effusion is present synovial fluid should be aspirated and analysed to exclude inflammatory disease and to identify urate and calcium pyrophosphate crystals. OA synovial fluid is typically non-inflammatory with <2000 leukocytes/mm\(^3\); if specifically sought, basic calcium phosphate crystals are often present.

Level of evidence: IIb, Strength of recommendations: 73 (95% CI 56-89)

Clinically evident effusion is not a typical clinical marker of knee OA although it may present in some severe or symptomatic cases. It is important to aspirate affected knees to determine whether there is coexistent crystal deposition or other disease. OA synovial fluid is typically non-inflammatory with
<2000 leukocytes/mm³. Larger volumes may associate with “apatite associated destructive arthropathy” although alizarin red staining (at acidic pH) of synovial fluid aspirated from OA knees commonly shows less plentiful basic calcium phosphate aggregates. The level of evidence to support this proposition is predominantly IIb.

Reference List


Figure 1. Study selection

**Inclusion criteria:**
1. Knee OA
2. Diagnosis issues
3. Clinical studies

**Exclusion criteria:**
1. Other arthritis or other joint OA
2. Progression
3. Therapy
4. Non-clinical researches (eg, DNA?)
5. Case reports, editorial or reviews

1738
MEDLINE: 337
EMBASE: 923
AMED: 478

134 duplicates

1604

1291 excluded because of
• treatment
• progression
• secondary validation (eg, the Spanish validation of WOMAC)
• non-OA studies
• non-clinical experiment (eg, genetics)
• case reports, reviews, editorial, or commentary
• animal studies

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Figure 2. Likelihood ratio and probability of knee OA (reference standard: radiographic KL≥2)
Figure 3. Clinical features and cumulative probability of radiographic knee OA – evidence from the UK population
Figure 4. Major components in the diagnosis of knee osteoarthritis
Notes

Advance online articles have been peer reviewed, accepted for publication, edited and typeset, but have not yet appeared in the paper journal. Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

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