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Suspected very early inflammatory rheumatic diseases in primary care

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A B S T R A C T

As primary care clinicians are typically the first point of contact for patients with musculoskeletal problems, they are crucial to the early diagnosis and treatment of patients with an incident inflammatory arthritis, like rheumatoid arthritis. Current UK and international guidelines recognise this, recommending the prompt referral of patients with suspected persistent synovitis to secondary care. In England and Wales, this is advised to occur within 3 working days. However, recent audit data suggests this recommendation is infrequently met, with some patients waiting many months for referral. In this review article we will discuss the various challenges to achieving the early referral of patients with a new-onset inflammatory arthritis from primary to secondary care. We will also describe how these challenges could potentially be overcome, with the ultimate goal of ensuring that the right patients are referred to the right services, and at the right time.

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Background

In the UK, primary care is widely regarded as the foundation upon which all National Health Service (NHS) care is based and is often described as the "jewel in the crown" of the health service. In the UK, over 90% of all patient clinical contacts are in primary care, with >5 million GP consultations taking place each week in 2015/2016 [1]. Musculoskeletal complaints constitute an important contributor to the primary care workload, with approximately 20% of adults consulting their GP every year for these issues [2]. Whilst the vast majority of these consultations are for osteoarthritis or soft tissue musculoskeletal disorders [3], GPs are typically the first point of contact for patients with a new-onset inflammatory rheumatic disease, like rheumatoid arthritis (RA). Consequently, primary care is crucial to the early diagnosis and prompt treatment of such individuals.

The last decade has seen a paradigm shift in the way that patients with inflammatory arthritis, particularly RA, are managed. Historically, such patients received first-line treatment with non-steroidal anti-inflammatory drugs (NSAIDs), moving to synthetic disease-modifying anti-rheumatic drugs (DMARDs) relatively late in the disease process [4]. Current treatment, however, now focuses on early intensive treatment with synthetic DMARDs within the "window-of-opportunity" [5–7]. This temporally transient window is defined as the first few months after the onset of RA symptoms, which is a pathologically distinct phase during which patient outcomes can be more effectively modulated by DMARD treatment [5]. Current recommendations from the National Institute for Health and Care Excellence (NICE) are that this should be within 3 months of a patient presenting with persistent synovitis [8]. There is good evidence that this achieves the best clinical outcomes for patients [9,10], minimises the societal costs of inflammatory arthritis for patients and their families, and is cost-effective for the NHS [11].

As synthetic DMARDs are usually initiated in secondary care by rheumatologists, and in an NHS-setting patients require a primary care clinician referral to be seen by Hospital specialists, GPs are crucial to both the early diagnosis and prompt treatment of patients with a new-onset inflammatory arthritis. As a consequence, current national and international guidelines recommend the prompt referral of patients with early inflammatory arthritis [12,13], with current recommendations from NICE advising that "people with suspected persistent synovitis affecting the small joints of the hands or feet, or more than one joint, are referred to a rheumatology service within three-working days of presentation" [8]. Despite this NICE recommendation, national audit data shows that most GP referrals to secondary care are delayed. Consecutive 2015 and 2016 Healthcare Quality Improvement Partnership (HQIP) Early Inflammatory Arthritis audits (assessing healthcare within England and Wales) showed that only 17%–20% patients were referred within 3 working days. In 2015, the median referral time was 34 days, with over one quarter of patients waiting more than 100 days [14]. In 2016, the median referral time was 20 days, with over one quarter of patients waiting more than 54 days [15]. Whilst delays to early DMARD initiation occur at multiple levels of a patients' journey – spanning the patient level, with patients delaying seeking medical advice for their symptoms, the primary care level, with primary care clinicians not recognising and referring such patients promptly, and the secondary care level, with rheumatologists not seeing patients in a timely manner or initiating DMARDs promptly [16] – these NHS HQIP data indicate that primary care referral delays are an important contributor to the overall delay.

In this review article we will discuss the various challenges to achieving the early referral of patients with a new-onset inflammatory arthritis from primary to secondary care. We will discuss how these challenges could potentially be overcome, with the ultimate goal of ensuring that the right patients are referred to the right services, and at the right time.

Current guidelines for referring new-onset inflammatory arthritis

Inflammatory arthritis is an umbrella term grouping several conditions together due to the shared feature of autoimmune-driven joint inflammation [17]. The main forms of inflammatory arthritis are RA, psoriatic arthritis (PsA), and axial spondyloarthritis (axial SpA), which together affect just over 1% of the UK population [18–20]. All three diseases can cause peripheral joint arthritis, although the dominant feature of axial SpA is spinal inflammation.

Whilst guidelines for primary care referrals will vary across countries, it is universally agreed that the early referral of patients with a new-onset inflammatory arthritis is crucial [13]. Using NHS-based recommendations as an exemplar, current NICE guidelines for referring patients with a suspected new-onset inflammatory arthritis consider peripheral and axial inflammatory arthropathies separately (Fig. 1). For patients with a peripheral inflammatory arthritis, NICE recommend urgent referral (within 3-working days) of patients with *any* of the following features: a) small joints of the hands and/or feet affected; b) more than one joint affected [8]. This is irrespective of the results of laboratory tests including inflammatory markers, rheumatoid factor and anti-cyclic citrullinated peptide antibodies (anti-CCP), with guidance suggesting that whilst these can be performed at the time of referral, they should not influence the decision to refer. Indeed, there is evidence detailed later in this review, demonstrating that negative investigations can be falsely reassuring to primary care clinicians, contributing to referral delays [21,22]. NICE use the term "suspected persistent synovitis" when describing a suspected new-onset peripheral arthritis. No precise definition as to what "persistent synovitis" represents is provided, although they note that symptoms and signs of persistent synovitis include pain, swelling, heat and early morning stiffness lasting over 30 min, which does not resolve within 3 or 4 weeks [8].

For referring patients with a suspected axial SpA, NICE recommend that patients are referred to a rheumatologist for a "spondyloarthritis assessment" if they have low back pain that started before the age of 45 years, has lasted for longer than 3 months, and have 4 or more of the following additional criteria [23]:

- lower back pain that started before the age of 35 years
- waking during the second half of the night because of symptoms
- buttock pain
- improvement with movement
- improvement within 48 h of taking non-steroidal anti-inflammatory drugs (NSAIDs)
- a first-degree relative with spondyloarthritis
- current or past arthritis
- current or past enthesitis
- current or past psoriasis

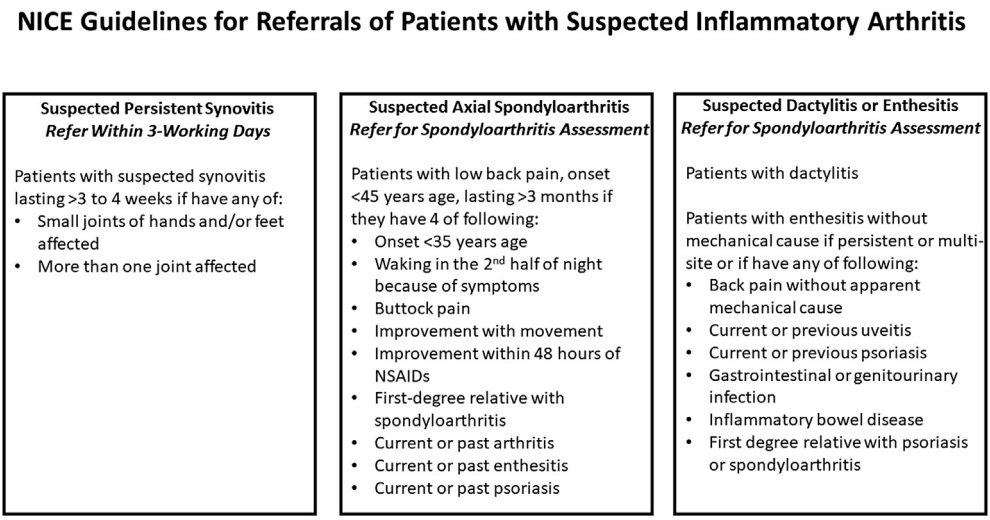

Fig. 1. National Institute for Health and Care Excellence (NICE) Recommendations for the Referral of Patients with a Suspected New-Onset Inflammatory Arthritis by Primary Care Clinicians. Figure produced using information reported within the online NICE quality standards for rheumatoid arthritis [8] and spondyloarthritis [23].

If exactly 3 of the above additional criteria are present, an HLA-B27 test is recommended, with referral suggested if this is positive.

In addition, NICE recommend referring patients with dactylitis to a rheumatologist for a "spondyloarthritis assessment" and patients with enthesitis without an apparent mechanical cause for a "spondyloarthritis assessment" if it is persistent or in multiple sites or if any of the following features are present:

- back pain without an apparent mechanical cause
- current or previous uveitis
- current or previous psoriasis
- gastrointestinal or genitourinary infection
- inflammatory bowel disease
- a first degree relative has psoriasis or spondyloarthritis

No specific time-frame is given for the urgency of the "spondyloarthritis assessment".

Barriers to the early referral of patients with a new-onset inflammatory arthritis

A broad range of barriers exist to the early referral of patients with a new-onset inflammatory arthritis from primary to secondary care. These span limited primary care clinician training and experience in assessing patients with incident inflammatory arthritis, the heterogeneous nature of early inflammatory arthritis, which can often present with non-specific symptoms and signs, current primary care workloads, the often transient nature of synovitis in patients seen in primary care, and the reliance of primary care practitioners on the use of investigations to inform their referral decisions.

Limited clinician experience in assessing new-onset inflammatory arthritis

One of the greatest challenges to GPs when identifying patients with a new-onset inflammatory arthritis is that this is a relatively rare clinical problem, and they will therefore have limited experience in seeing such patients. Whilst the main forms of inflammatory arthritis (RA, PsA, and axial SpA) have a combined prevalence of just over 1% of the UK population [18–20], the estimated annual incidence of RA, which is the commonest type of inflammatory arthritis, is only 15–40 cases per 100,000 adults [24,25]. Therefore, the average full-time GP can only expect to encounter approximately one new case of RA every 1–2 years [26]. The rarity of incident inflammatory arthritis is compounded by the high primary care consultation rates for patients with musculoskeletal pain within the UK. In an analysis of a large primary care electronic health record dataset based in North Staffordshire, England (the CiPCA database), Jordan et al. estimated the consultation prevalence of musculoskeletal conditions per 10,000 registered population to be 4914 over a 7-year period (between January 2004 and December 2010); the consultation prevalence for RA, ankylosing spondylitis and psoriatic arthritis was just 48, 8, and 10, respectively [3]. This makes correctly identifying and referring patients with a new-onset inflammatory arthritis very challenging, as although musculoskeletal problems are common, new diagnoses of inflammatory arthritis are rare.

GP rheumatology training

Aligned with this limited clinical exposure, is the problem that medical students, junior doctors and GPs receive limited training in rheumatology. In 1992, Lanyon et al. highlighted this issue in a survey of 1624 GP trainees across the UK [27]. Of the 1075 responders at the end of their trainee year, 35% had not received any tutorials on rheumatology topics with their trainer, and only 43% had experienced specific rheumatology teaching on local day release courses. Despite repeated efforts to improve rheumatology training for under-graduate and GP trainees, the level of rheumatology teaching provided in the curriculum remains unchanged for the last 2 decades [28]. The issues with training primary care clinicians in rheumatology have been further highlighted in a multi-region survey and national audit. In a multi-region survey spanning 5 English training regions (deaneries), 147 GP trainees were asked to self-rate

their rheumatology and musculoskeletal training (Fig. 2). Of these, 56% rated the rheumatology tuition and information content of their GP training to be "poor or very poor", and 46% rated their confidence at managing inflammatory arthritis as "not all confident or lacking confidence" [29]. In a 2009 National Audit Office survey of GPs about the diagnosis and management of RA [30], from 481 surveyed GPs, 27% answered "no" to the question "did your pre-registration training cover rheumatoid arthritis?". Of those receiving training, 66% described it as being "brief" and 21% and 3% stated that this training prepared them to recognise the symptoms of RA "not very well" and "not at all well", respectively. Limited rheumatology training amongst primary care clinicians appears to be a universal issue, with previous surveys of "family medicine" residents and programme directors in North America highlighting perceived rheumatology training inadequacies [31,32].

Non-specific symptoms in new-onset inflammatory arthritis

Another important challenge in identifying patients with a new-onset inflammatory arthritis is that such patients may present with non-specific symptoms, particularly in the earliest phases of the disease process. This is highlighted in a qualitative study by Stack *et al*, which involved interviews with 11 patients with early RA, and 15 patients with arthralgia and positive anti-CCP antibodies at a high-risk of progression to established RA. Whilst symptoms of joint pain, swelling and stiffness were common, patients also reported symptoms that are not specific to inflammatory arthritis, including numbness, restricted movement, loss of strength, sudden loss of function, muscle fatigue, muscle cramps, abnormal skin sensations, weight loss and burning sensation, warmth and redness around their joints [33]. Similarly, a systematic literature review of qualitative studies by the same researchers highlighted the presence of non-specific symptoms in other studies of patients with early RA [34]. This systematic review identified 26 studies meeting the researchers' inclusion criteria of "qualitative studies using an interpretative paradigm to understand the descriptions of symptoms experienced by adults at RA onset". Five major themes of symptom complexes were identified. Whilst three of these were traditional themes associated with RA (pain and tenderness, swelling, stiffness) two others were non-specific (fatigue and weakness; emotional impacts). Examples of quotes from patients relevant to these latter two themes include: "First noticed there was a problem, there was a weakness in the hands. Just slight weakness" and "But what I do remember about the beginning of the rheumatoid arthritis was the massive weariness being almost, almost the biggest symptom".

Presence of possible inflammatory arthritis symptoms in the general population

A recent survey by Hider et al. has highlighted the problem that patients seeing their GP for non-musculoskeletal problems also frequently self-report (by questionnaire) symptoms suggestive of an

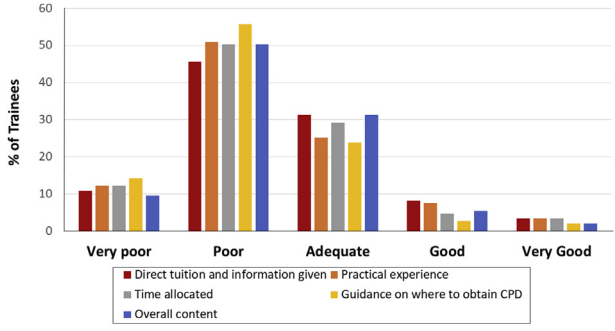

Fig. 2. Final Year GP Trainees' Rating of the Rheumatology Content of their GP Training In Five English Training Regions Undertaken in 2012. Final year (ST3) GP trainees were asked to rate the following aspects of their rheumatology training on a five-point scale (1 = very poor, 5 = very good): direct tuition and information given; practical experience; time allocated; guidance on where to obtain CPD (continued professional development); overall content. Figure produced using data reported by Bajkowski and Warburton at the British Society of Rheumatology Annual General Meeting [29].

inflammatory arthritis. In this study, a self-completion questionnaire was sent to over 10,000 patients consulting their GPs for both musculoskeletal and non-musculoskeletal complaints [35]. Whilst symptoms that were suspicious of an inflammatory arthritis were commoner in those patients consulting their GP for musculoskeletal problems, 75%, 37% and 64% of patients consulting their GPs for non-musculoskeletal issues also reported having joint pain, joint swelling and joint stiffness, respectively. Further studies are required to determine what proportion of these patients also have joint swelling on clinical assessment.

Presence of inflammatory arthritis symptoms in patients with medically unexplained symptoms

Approximately 3–10% of all adult patients presenting in a primary care setting will have persistent or recurrent medically unexplained symptoms [36], which can be broadly defined as physical symptoms in the absence of a cause found on clinical examination or investigation [37]. Patients can represent multiple times with these symptoms seeking an explanation, and as a result primary care practitioners can feel pressured into providing a physical explanation for their symptoms, rather than a psycho-somatic explanation [38,39]. Such individuals often have symptoms suggestive of a new-onset inflammatory arthritis, like pain and fatigue. Excluding a new-onset inflammatory arthritis in such individuals is very challenging for primary care clinicians, and often results in onward referral to secondary care services.

Burden of work in primary care

Over the last decade, the workload of GPs has steadily increased. There has been a growth of approximately 10.5% in the volume of GP and primary care nurse practitioner consultations [40], with an analysis undertaken by the Kings Fund reporting that in 177 primary care practices, the number of consultations increased by over 15% between 2010/11 and 2014/5 [41]. Aligned with the increased volume and complexity of patients being seen (due to the ageing population and increasing multimorbidity) is the fact that primary care practices are finding it harder to retain and recruit clinicians. The end result is that patients find it harder to obtain appointments and have a longer wait (often of several weeks) for routine reviews. NHS England has tried to counter some of these issues in its publication "General Practice forward view" [42] by encouraging GP practices to work together and diversify the workforce by using other health-care practitioners (including nurses) to expand the breadth of their clinical skills, and see more patients independently. Unfortunately, these factors conspire to make it harder for patients with a new-onset inflammatory arthritis to have prompt appointments with their GPs, and when an appointment is arranged it may be with a non-medical practitioner such as a nurse, physiotherapist or paramedic, who may be unfamiliar with diagnosing new-onset inflammatory arthritis.

The transient nature of synovitis in patients seen in primary care

An analysis of primary care records from four primary care practices within the Netherlands has highlighted the transient nature of synovitis in many patients seen in a primary care setting [43]. The research team reviewed the case records of incident cases of patients with a diagnosis of "non-specific arthritis" (defined as all types of inflammatory arthritis except RA and gout) occurring between 1990 and 2004, in whom at least 5 years of follow-up data were available. The incidence of non-specific arthritis was 3.1 per 1000 patients per year. 362 patients had an episode of non-specific arthritis, of whom 88% had a monoarthritis. 62 patients died during the follow-up period, providing 300 patients with 5 years of follow-up data available for analysis. Of these individuals, the vast majority (81%) were only seen on a single occasion or received one further follow-up review (Fig. 3). The authors concluded that these patients were likely free of subsequent arthritis-related complaints, with no indication in their records that they were managed elsewhere subsequently.

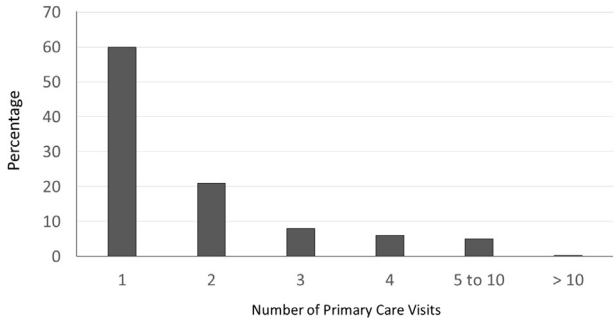

Fig. 3. Number of Primary Care Visits in 300 Patients Diagnosed with "Non-Specific Arthritis" in the Netherlands. Data are from 300 patients seen in four primary care practices in the Netherlands. Incident cases of non-specific arthritis are included from 1990 to 2004. Patients are excluded if they have <5 years' follow-up data available. Non-specific arthritis is defined as all types of inflammatory arthritis except RA or gout. Figure produced using data reported by Knuiman and Schers [43].

The use of investigations to inform referral decisions

One core aspect of a GP's role is to act as a "gate-keeper" to secondary care services, rationing referrals, so that appropriate patients are referred to the correct services in a timely manner, avoiding unnecessary referrals to secondary care. There is good evidence that GPs use serological tests (chiefly rheumatoid factor) to either confirm or exclude a diagnosis of RA, before referring patients with a new-onset inflammatory arthritis to secondary care. This practice was highlighted in a GP survey (the RA Questionnaire [RA-QUEST] study), which had responses from 1388 GPs working in England about the challenges they face in diagnosing and referring patients with suspected RA [44]. Of those GPs surveyed, 74% said they would request investigations to inform their referral decision in a patient in whom they suspected RA, with 95% of those requesting investigations stating they would perform a rheumatoid factor test. Similar findings highlighting the use of investigations were demonstrated in two other studies. Firstly, Cottrell et al. undertook a case-note review of 24 incident cases of inflammatory arthritis at a Staffordshire GP practice in order to evaluate factors influencing referral delays [21]. They reported that 92% of patients had laboratory tests prior to referral, and 46% of patients had at least one radiograph performed. Secondly, Pollard et al. undertook a series of patient, carer, outpatient staff, and GP focus groups and face-to-face interviews, aimed at identifying perceived barriers to providing integrated care for patients with RA [45]. From 37 patients, 4 reported their referral depended on positive blood tests. From 13 GPs, 11 reported waiting for "positive blood tests" for rheumatoid factor before referring. Two key quotes highlighting this practice from separate GPs are: "If you don't do the blood test the hospital would be absolutely overwhelmed. If everybody [patient] who thought they might have rheumatoid we refer to hospital, the system would grind to a halt" and "So we normally do blood tests like RA Factor and antibodies and when they come back and yes the suspicion is that they might have RA, then we refer".

This practice of using investigation results to inform referral decisions, whilst entirely understandable, will inevitably lead to most patients with a suspected new-onset inflammatory arthritis failing to be referred within the NICE recommended time-frame of 3 working days, due to the process of phlebotomy, laboratory testing, and results reviewing often taking several days to weeks. Of additional concern is that there is evidence that negative rheumatoid factor and X-ray results are falsely reassuring to GPs, reducing either the likelihood of patients being referred or the timeframe in which they are referred. Firstly, in the case-review by Cottrell et al. (discussed above) the mean duration to referral for patients with RA with radiographs performed was 966 days compared to 166 days for those without ($P = 0.014$), suggesting normal radiographs were falsely reassuring [21]. Secondly, Sinclair et al. surveyed 200 GPs making requests for rheumatoid factor at a single laboratory. 66% of GPs receiving a negative rheumatoid factor result vs. 25% of those receiving a positive rheumatoid factor result stated they "will not refer at present" [46]. Thirdly, Miller et al. conducted an analysis in the Clinical Practice Datalink (CPRD), a large primary care electronic database representing 8% of the UK

population. Patients with confirmed RA in whom rheumatoid factor tests were performed 2 years prior to their diagnosis were identified. The median time to referral for those with a negative rheumatoid factor test was 67 days vs. 22 days in those with a positive rheumatoid factor test ($P < 0.001$) [22].

What can be done to facilitate prompt referrals?

The barriers described above highlight the need for a multi-faceted approach to change the referral practice of GPs for patients with new-onset inflammatory arthritis, so that most patients are referred within the 3-working day timeframe recommended by NICE. This could involve increased clinician training designed to increase GP self-efficacy at identifying patients with synovitis, clinical decision aids, and the use of novel health service approaches like the adoption of early arthritis recognition clinics [47].

Primary care clinician training

There is evidence that the targeted education of primary care practitioners can improve the referral process for patients with a suspected inflammatory arthritis. An American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) taskforce undertook a systematic review of strategies to reduce the delays in the diagnosis and treatment of patients with a new-onset inflammatory arthritis in 2012. This review identified 8 studies that focused on primary care practitioner education programmes [48]. These education programmes comprised workshops, joint consultations with rheumatologists, tele-clinics, and educational material. All studies reported that these approaches had some success in improving the knowledge and ability of practitioners to detect inflammatory arthritis and/or the quality of referrals. Since this review was published, an additional study demonstrated the benefits of a targeted education program in increasing referral rates in simulated patients with an axial or peripheral spondyloarthritis [49]. In this study, the proportion of GPs that would refer or consider referral of a simulated patient with features of an axial SpA increased from 6% to 77%, and with features of a peripheral SpA increased from 5 to 53%, following the educational intervention.

The British Society for Rheumatology have recognised the challenges that primary care clinicians face in recognising new-onset inflammatory arthritis and have developed an educational resource aimed at improving primary care clinician knowledge in this area. The “Inflammatory Arthritis Toolkit” was developed in collaboration with the Royal College of General Practitioners [50]. It is freely available online (at: https://www.rcgp.org.uk/clinical-and-research/resources/toolkits/inflammatory-arthritis-toolkit.aspx) and brings together E-learning guides on the types of inflammatory arthritis, programmes on how to examine the musculoskeletal system (prepared by the charity Versus Arthritis), core skills, and Podcasts with patients and Rheumatology Specialist Nurses.

Change in referral practice to using clinical findings in patients with synovitis

As an important modifiable barrier to prompt referrals is the widespread practice of using investigations (like rheumatoid factor) to inform referral decisions, changing the way referral decisions are made is crucial. Patients with active inflammatory arthritis may have normal inflammatory markers; additionally, approximately one third of RA patients are seronegative for rheumatoid factor and anti-CCP antibodies [51], therefore using these results to inform referral decisions is inappropriate. This is recognised by NICE, who recommend that “any person with suspected persistent synovitis of undetermined cause whose blood tests show a normal acute-phase response or negative rheumatoid factor should still be referred urgently as they may still have rheumatoid arthritis” [8]. Therefore, changing GP referral practice so that referrals are made on clinical grounds in patients with synovitis is required. The optimal manner to do this is unclear and is likely to require a complex intervention that increases GP's self-efficacy at identifying synovitis based on history and examination findings. Further research in this area is urgently required, which includes the impact on secondary care services as such an approach is likely to increase the number of referrals of patients from primary to secondary care.

Developing decision aids in patients with clinically suspect arthralgia

Clinicians often encounter patients with arthralgia without synovitis. Many conditions cause arthralgia, such as osteoarthritis, and soft tissue disorders. Clinical judgment is required to establish which of these patients with arthralgia are likely to develop an inflammatory arthritis. Whilst rheumatologists have been demonstrated in a recent Dutch study to have good accuracy at identifying patients with arthralgia that are likely to develop RA [52], it is challenging for non-specialists to identify such patients [53]. The development of clinician decision aids that primary care clinicians could use in patients with arthralgia to identify those at high-risk for progression to an inflammatory arthritis requiring urgent referral would be helpful in this regard. A European League Against Rheumatology (EULAR) task-force has recently developed a points-based definition for patients with arthralgia suspicious for progression to RA [54]. Seven parameters were included in their definition (Table 1). The presence of $\geq$3 parameters had a 90% sensitivity for identifying patients that experts would classify as being at high-risk of progression to RA; the presence of $\geq$4 parameters had a specificity >90%. This definition was, however, developed for use in a secondary care setting. Further research is required to evaluate its performance in a primary care environment.

Screening patients with non-specific musculoskeletal symptoms

It is widely accepted that patients with RA undergo a series of "pre-clinical" phases prior to the development of an established RA phenotype. These have been defined by the EULAR study group for risk factors for RA [55]. This group defined six phases underlying the preclinical and earliest clinically apparent phases of RA, comprising Phase A, genetic risk factors for RA; Phase B, environmental risk factors for RA; Phase C, systemic autoimmunity associated with RA; Phase D, symptoms without clinical arthritis; Phase E, unclassified arthritis; and Phase F, early RA. It is noted that patients do not pass through all phases. A study by Nam et al. evaluated the role of using serological testing in patients in phase D (symptoms without clinical arthritis) in primary care [56]. This study assessed the role of anti-CCP testing in predicting which patients with new musculoskeletal symptoms but without synovitis are likely to progress rapidly to an inflammatory arthritis. In this prospective cohort study, 2028 individuals from primary care with new non-specific musculoskeletal symptoms were recruited and tested for anti-CCP. Of these, 2.8% of individuals were positive for anti-CCP, of whom 47% developed an inflammatory arthritis (median time to onset 1.8 months). From the anti-CCP negative individuals, 1.3% developed an inflammatory arthritis (median time to onset 5.1 months). The relative risk of developing RA within 12 months in the anti-CCP positive group was 66.8 (95% CI 32.2 to 138.4). Whilst these data suggest that anti-CCP testing could be a useful tool in identifying patients with musculoskeletal symptoms likely to progress to an inflammatory arthritis, the cost-effectiveness of this approach is unknown, with further research required in this area, before such case-finding strategies could be considered in routine care.

Table 1
Seven parameters included in the EULAR definition for patients with arthralgia suspicious for progression to rheumatoid arthritis [54].

History	(1) Symptom duration <1 year
	(2) Symptoms in metacarpophalangeal (MCP) joints
	(3) Morning stiffness duration $\geq$60 min
	(4) Most severe symptoms in early morning
	(5) First-degree relative with RA
Examination	(6) Difficulty with making a fist
	(7) Positive squeeze test of MCP joints

The parameters are to be used in patients with arthralgia without clinical arthritis and without other diagnosis or other explanation for their arthralgia. The presence of $\geq$3 parameters has a 90% sensitivity for identifying patients that experts would classify as being at high-risk of progression to RA; the presence of $\geq$4 parameters has a specificity >90%.

Triage tools for suspected new-onset inflammatory arthritis

One of the challenges in delivering early synovitis clinics is ensuring that the correct patients (those that are likely to have a new-onset inflammatory arthritis) are seen in them. Prioritising patients for these rapid access appointments can be challenging and relies on robust primary care assessment to ensure that the right patients are recognised and referred. To further aid this process, several triage tools have been developed that attempt to discriminate between patients referred to secondary care that are likely to have an inflammatory arthritis, and those that are likely to have other causes for their musculoskeletal symptoms. One example is the Early Inflammatory Arthritis (EIA) detection tool, which is a self-reported questionnaire that asks patients 11 questions (with binary yes/no responses) about symptoms relevant to having a peripheral inflammatory arthritis (Table 2). This questionnaire was developed following a systematic literature review, and Delphi consensus panel of international experts and stakeholders [57,58]. It can be scored either using the sum of the number of positive responses [57], or using a weighted scoring algorithm [58]. A higher score on the EIA detection tool (using either scoring mechanism) suggests a higher likelihood of a patient having a peripheral inflammatory arthritis. In a secondary care setting, the tool displays a favourable ability to discriminate between patients with and without a peripheral inflammatory arthritis (area under the curve of 0.83) [58]. In a primary care setting, the EIA detection tool has been shown to be more sensitive, but less specific, than a primary care clinician's diagnosis. Tavares et al. evaluated 139 patients with 6–52 weeks of musculoskeletal complaints seen in a primary care setting [59]. All patients completed the EIA detection tool and received a rheumatology consultation regardless of if they were referred by a primary care clinician. Nineteen patients received a rheumatologist diagnosis of an inflammatory arthritis. The EIA detection tool was considerably more sensitive, but also less specific, at identifying patients with a rheumatologist confirmed diagnosis of an inflammatory arthritis (sensitivity 0.79 [95% CI 0.61 to 0.97]; specificity 0.58 [95% CI 0.49–0.66]) compared to a primary care clinician's diagnosis of inflammatory arthritis (sensitivity 0.26 [95% CI 0.07 to 0.46]; specificity 0.89 [95% CI 0.84–0.95]) [59]. Further evaluation of the performance of this tool is required, in larger patient groups and more diverse healthcare settings, before its use in routine practice could be considered.

Adoption of early arthritis recognition clinics

Another approach is to change the nature of the interaction between primary and secondary care clinicians for patients with a suspected new-onset inflammatory arthritis. The current model of care widely adopted across the UK is that primary care clinicians can refer patients to dedicated “Early Synovitis Clinics”, which have ring-fenced dedicated appointments for patients with suspected persistent synovitis, allowing prompt secondary care reviews.

An alternative to Early Synovitis Clinics, which has been undertaken since 2010 in Leiden and Groningen (Holland), is to use “Early Arthritis Recognition Clinics” (EARCs) [47]. Using this model of

Table 2
Eleven questions used in the early inflammatory arthritis detection tool [57,58].

Early Inflammatory Arthritis Detection Tool Item
1. Do you have pain in your joints?
2. Do you have pain in your wrists and hands?
3. Are your hands or wrists swollen?
4. Do you have trouble making a fist?
5. Are your joints stiff in the morning?
6. From the time you wake in the morning, does it take more than 60 min for your joints to move more freely?
7. Are the same joints involved on both sides of your body?
8. Have important activities in your life been affected because of bone or joint problems, such as having difficulty with personal care or having to make a change regarding leisure or work activities?
9. Have you ever been told that you have rheumatoid arthritis?
10. Does anyone in your family have rheumatoid arthritis?
11. Have you been diagnosed with a rash called psoriasis?

The tool should be used in patients with symptoms for more than 6 weeks and less than one year.

care, GPs send patients they suspect have an inflammatory arthritis to the EARCs where patients can walk-in without the need for a formal appointment or waiting list. Patients report their symptoms on brief self-completed questionnaires, including a joint mannequin and subsequently rheumatologists perform a brief (5–10 min) musculoskeletal examination for synovitis in each patient. Standard 1-week outpatient appointments are given to patients with confirmed synovitis, and patients without synovitis are discharged. EARCs have been demonstrated to reduce delays between patients first seeing their GP with symptoms of arthritis and being assessed by a rheumatologist. At Leiden and Groningen, the median delays are 2-weeks with the EARCs, but 9–11 weeks with standard early synovitis clinics [47]. The acceptability of this approach to patients and clinicians, and their cost-effectiveness, however, requires further study. Further research is therefore required to assess this before their more widespread implementation could be considered in a routine clinical setting.

Improved working relationships across the primary-secondary care interface

Improving primary care clinicians' access to rapid specialist advice in patients with suspected new-onset inflammatory arthritis is also important. The RA-QUEST study suggests this represents a significant issue, with 25% of surveyed GPs rating their ease of access to rheumatology as being $\leq$5 out of 10 [44]. Advice and Guidance schemes could be helpful in this regard. These schemes represent non-face-to-face activity with specialists giving advice to GPs either as real-time telephone advice, or asynchronous advice carried out electronically (e.g. through the NHS e-Referral Service) [60]. Advice and Guidance schemes are intended to "help ensure patients are seen and treated in the right place, at the right time as quickly as possible" and "help GPs make a better and more informed decision on the most appropriate course of action for their patients". They are being increasingly adopted in the NHS, as they represent one aspect of the Commissioning for Quality and Innovation (CQUIN) scheme for 2017–2019 [61], providing a financial incentive for secondary care services to undertake them.

Summary

Primary care clinicians are crucial to the early diagnosis of patients with a new-onset inflammatory arthritis, acting as the initial contact for newly presenting patients in the vast majority of cases. However, UK Early Inflammatory Arthritis audit data has highlighted that in England, a minority of patients with suspected persistent synovitis are referred by GPs within the NICE recommended timeframe of 3-working days. Research has highlighted numerous barriers to the early referral of such patients, with two key, inter-related barriers being a lack of GP confidence at identifying patients with synovitis and RA, and their consequent reliance on investigations (chiefly rheumatoid factor) to inform their decision to refer patients for specialist review. Urgent further research is required to determine how to change this referral practice, so that most patients with a new-onset inflammatory arthritis are referred for urgent specialist review, without a consequent increase in referrals of patients with other musculoskeletal conditions to early synovitis clinics. In addition, the diagnostic performance of decision aids and triage tools, that help primary care practitioners identify patients with a new-onset inflammatory arthritis, or arthralgia at a high risk of progression to RA, require evaluation in a primary care setting.

Practice points

- Identifying patients with a new-onset inflammatory arthritis in primary care is very challenging, with a recent survey showing that many patients not consulting their GP for musculoskeletal problems also report symptoms suggestive of an inflammatory arthritis, like joint swelling.
- Primary care practitioners often use investigations like rheumatoid factor and radiographs, to "identify" patients with an incident inflammatory arthritis before referring them to secondary care.
- There is evidence that negative test results are falsely reassuring to primary care practitioners, leading to delayed referrals of patients with rheumatoid arthritis.

Research agenda

- Studies are required to establish how to change the referral practice of primary care practitioners so that they refer patients with persistent synovitis on clinical grounds, as opposed to relying on investigation results, which can be falsely negative.
- Research should also focus on the impacts of this referral approach on secondary care services, as it will inevitably result in higher referral rates.
- The diagnostic performance of decision aids and triage tools, that help primary care practitioners identify patients with a new-onset inflammatory arthritis, or arthralgia at a high risk of progression to rheumatoid arthritis, require evaluation in a primary care setting.

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Conflicts of interest

The authors report no relevant conflicts of interest.

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