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PART I
Early recognition of arthritis
CHAPTER 2
Improved early identification of arthritis: evaluating the efficacy of Early Arthritis Recognition Clinics

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ABSTRACT

Objective
Only 31% of Dutch rheumatoid arthritis (RA)-patients visit a rheumatologist within 12 weeks after symptom onset; this is mainly due to delay at the level of the general practitioner (GP). In order to reduce delay of GPs in identifying early arthritis, we initiated an Early Arthritis Recognition Clinic (EARC).

Methods
EARCs were initiated at the Leiden and Groningen University Medical Centers. At this EARC, patients filled in a questionnaire about their symptoms, followed by a short visit with only a full joint examination by an experienced rheumatologist. If arthritis was present the patient got an appointment the same week at the regular outpatient clinic. The main outcome parameter was the GP-delay; the secondary outcome parameter was the total delay. In both centers, patients included in early arthritis clinics that had arrived via regular referrals served as control group.

Results
Four hundred patients visited the Leiden EARC and 212 patients the Groningen EARC. Arthritis was detected in 42% and 49% respectively. The median GP-delay for these arthritis patients was 2.0 (0.4-7.3) and 2.0 (0.4-10.0) weeks and the median total delay 8.6 (3.6-22.3) and 10.6 (3.1-30.8) weeks respectively. At these two clinics 59% and 51% of all arthritis patients and 65% and 53% of the patients that were subsequently diagnosed with undifferentiated arthritis or RA were seen within 12 weeks after symptom onset. In the Leiden and Groningen control groups that arrived via regular referrals, only 32% and 38% were seen within 12 weeks time.

Conclusions
The EARC increased the early identification of arthritis and RA.
INTRODUCTION

Data of multiple observational cohorts and clinical trials indicate that early initiation of aggressive treatment in rheumatoid arthritis (RA) patients results in a better outcome. RA-patients that were treated very early in the disease course more often developed remission and had less joint damage. This so-called ‘window of opportunity’ for treatment is estimated to encompass about the first 12 weeks after symptom onset. Therefore, recognizing arthritis within the first 12 weeks after symptom onset is essential.

We recently observed that only 31% of Dutch RA-patients visit a rheumatologist within 12 weeks after symptom onset. In the Dutch system, general practitioners (GPs) control the access to specialists such as rheumatologists. We also observed that delay at the level of the GP was the main contributor to the total delay, as it encompassed about two-third of the total delay of 18.4 weeks (median). This observation is in line with Dutch data revealing that GPs have difficulties in recognizing arthritis of small joints and that in case of doubt they apply a ‘wait-and-see’ approach. The distribution between patient delay and GP-delay may be different between countries or settings. Nonetheless, a recent study in 10 centres across Europe showed that there is a substantial delay between symptom onset and the first visit to the rheumatologic outpatient clinic, with the median total delay ranging between 16 and 38 weeks. Also, in a recently initiated immediate access clinic in Vienna the median symptom duration at first visit of RA-patients was 9 months.

We aimed to increase the proportion of arthritis and RA-patients that is identified within the first 12 weeks after symptom onset. Given the local situation, we particularly aimed at decreasing the GP-delay. To this end we initiated Early Arthritis Recognition Clinics (EARC) at two university medical centres in the Netherlands. GPs were advised to send any patient for which they were doubtful about the presence of arthritis to the EARC, instead of applying a ‘wait-and-see’ approach. At the EARC patients were, during a short visit, screened on the presence of arthritis by physical examination by experienced rheumatologists. This study investigated the efficacy of the EARC to decrease the GP-delay and consequently reduce the total delay in identifying arthritis.

PATIENTS AND METHODS

Early Arthritis Recognition Clinic (EARC)
This clinic started in September 2010 in Leiden and in October 2010 in Groningen, the Netherlands. Before we started, there was an educational campaign among regional GPs in Leiden and Groningen, focusing on the importance and the methods of identifying arthritis and the purpose of the EARC. The campaign included articles in GP-oriented
journals, lectures and discussions at periodic trainings of GPs and correspondence to GPs. No campaign was held at the level of the general public. GPs were advised to send any patients for which they had a clinical suspicion of arthritis but were doubtful of the presence of arthritis to the EARC, instead of applying a ‘wait-and-see’ approach. There were no formal inclusion or exclusion criteria. All patients that visited the EARC during the first 15 months were included in this study. The EARC is held 2 times a week. Patients, referred by their GPs, can visit the EARC without making an appointment. A referral letter is not required, though was generally provided by the GPs. This screening clinic has no waiting list. The EARC, a screening clinic aiming to improve early detection of arthritis, is different from the Leiden Early Arthritis Clinics (EAC) that includes and follows patients with, by a rheumatologist confirmed, early arthritis. Thus the subgroup of arthritis patients identified at the EARC can subsequently be included in the EAC. The Leiden University Medical Center is the only referral center in a health care region of ~400 000 inhabitants in the western part of the Netherlands. The University Medical Center of Groningen is situated in the northern part of the Netherlands and is one of two referral centers in a health care region of ~700 000 inhabitants. The University Medical Center of Groningen also has an EAC that includes patients suspected of having arthritis. In both areas patients had equal access to a GP. In the area of Leiden there was one full-time equivalent GP available per 2400 inhabitants and in the area of Groningen this was one per 2383 inhabitants.¹²

At the EARC patients complete a questionnaire about their joint symptoms, their reasons for seeking medical help and a HAQ (for further details see ¹³). Hereafter, they are seen by an experienced rheumatologist who performs a full joint examination. In case arthritis is present, patients visit the general outpatient clinic, within 1 week time for further examinations, inclusion in the EAC after informed consent and appropriate treatment.¹⁴

**Outcome**

The main outcome that is relevant for determining the efficacy of the EARC was the GP-delay. Secondary outcomes were the total delay and the proportion of patients that had a total delay of less than 12 weeks. The total delay was defined as the period between the by patient reported symptom onset and the first visit to the rheumatologic outpatient clinic. It is composed of the patient delay and GP-delay. The GP-delay was defined as the time between the first visit to the GP and the first visit to a rheumatologist. As the EARC has no waiting list, it mainly represents the time the GP takes to refer a patient to the rheumatologist.

In order to evaluate the efficacy of the EARC two comparisons were made. The first was between EARC patients and patients that were included in the Leiden and Groningen Early Arthritis Clinics and had arrived by regular referrals at the same time period as the
EARC was present. This comparison may be relevant since an educational campaign was held and a reduction in delay may be attributable to both education and the EARC itself. If, hypothetically speaking, the GP-delay would mainly be affected by the educational campaign – and not by the EARC – the GP-delay of patients that came via regular referrals might also decrease. Alternatively, if the EARC would be the most effective strategy, it was hypothesized that the GP-delay of the patients that visited the EARC would be shorter than the GP-delay of patients that came via regular referrals. The second comparison was a historical comparison and could only be applied to the Leiden dataset. The GP-delay and total delay in early arthritis and early RA-patients included between 1993 and 2006 in the Leiden EAC and thus before the institution of the EARC were compared to the EARC data. For a full overview of patients studied please see figure 1.

The outcomes were assessed for all early arthritis patients and for patients that were diagnosed as undifferentiated arthritis (UA) or RA at the subsequent regular outpatient clinic visit. RA was classified using the 2010 ACR/EULAR classification criteria.15

**Figure 1.** Flowchart of patients with joint symptoms who were screened at the Leiden and Groningen Early Arthritis Recognition Clinics (EARCs) during the first 15 months.

**Legend Figure 1.** With regard to the control group, presented are the number of patients that were included in the Early Arthritis Clinics of both centers and that arrived via regular referrals. The total numbers of patients who visited the outpatient clinic of the LUMC or UMCG have not been counted. LUMC, Leiden University Medical Center; UMCG, University Medical Center of Groningen. Rheumatoid arthritis (RA) is classified according to the 2010 criteria at the first regular outpatient clinic visit. Since it is in this very early disease phase often challenging to definitely discern between undifferentiated arthritis (UA) and RA, these two patient-sets were analysed together.
**Statistical analysis**
Comparisons were made using the $\chi^2$ test, Student t-test or Mann-Whitney U-test as applicable. SPSS software V.17.0 was used. p values less than 0.05 were considered significant.

**RESULTS**

**Baseline characteristics**
During the first 15 months, 400 patients visited the Leiden EARC and 212 patients the Groningen EARC. Arthritis was observed via physical examination in 168 (42%) patients screened in Leiden and in 104 patients (49%) screened in Groningen. The baseline characteristics are presented in table 1. The diagnoses made during the first regular outpatient clinic visit were: RA (Leiden 14.3%, Groningen 9.6%), UA (Leiden 35.1%, Groningen 32.7%), inflammatory osteoarthritis (Leiden 18.5%, Groningen 26.9%), crystal-induced arthritis (Leiden 7.8%, Groningen 5.8%), psoriatic arthritis (PsA) or spondyloarthritis (SpA) (Leiden 4.2%, Groningen 6.7%) and other diagnoses (Leiden 20.1%, Groningen 18.3%).

In order to make comparisons, patients included in the Early Arthritis Clinics, that had arrived via regular referrals were studied (n=116 and n=147 respectively, table 1). These patients had the following diagnoses: RA (Leiden 33.6%, Groningen 17.0%), UA (Leiden 33.6%, Groningen 11.6%), PsA or SpA (Leiden 15.5%, Groningen 5.4%), inflammatory osteoarthritis (Leiden 8.6%, Groningen 14.8%) and crystal arthritis (Leiden 2.6%, Groningen 10.9%), other diagnoses (Leiden 6.8%, Groningen 36.4%).

Dates on symptom onset were missing for 5 and 14 arthritis patients in Leiden and Groningen EARCs respectively and dates on the first visit to the GP were not available for 18 and 9 patients respectively. For the control groups, dates on symptom onset were missing for 1 and 34 patients in Leiden and Groningen and dates on the first GP visit were not available in 27 and 55 patients respectively.

The Groningen control group was used for comparisons on all early arthritis patients but considered too small for sub-analyses on UA-patients and RA-patients (only 19 UA-patients and RA-patients had complete data).

**GP-delay of early arthritis patients**
When evaluating all patients screened at the EARCs, the median GP-delay was 2.0 (0.4-8.4) weeks in Leiden and 2.3 (0.6-9.1) weeks in Groningen. Since the aim was to more frequently identify arthritis at an early stage, the delay of patients with arthritis was studied more extensively (figure 2A). In the Leiden EARC arthritis patients, the median
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GP-delay was 2.0 (0.4-7.3) weeks in contrast to 9.4 (5.9-23.2) weeks in the Leiden arthritis patients who arrived at our clinic via regular referrals. Thus indicating a difference of about 7.4 weeks, p<0.001. The median GP-delay of early arthritis patients identified via the EARC was also considerably lower than the historical GP-delay which was 8.0 (2.7-18.4) weeks.(8) The median GP-delay in the Groningen EARC arthritis patients was 2.0 (0.4-10.0) weeks which was comparable to the Leiden EARC data, and lower than the GP-delay of the patients that arrived via regular referrals in Groningen which was 3.9 (2.6-12.8) weeks (p<0.001). The GP-delay was rather stable during the study period (see online supplementary figure S1).

Figure 2. General practitioner-delay (A) and total delay (B) of patients with arthritis and without arthritis screened at the Leiden and Groningen EARC.

Legend Figure 2. The delays of the patients that arrived via regular referrals were presented as well. Each data point represents a single patient; the black horizontal lines show the median.; In (A) 22 data points are out of range (arthritis n=8, no arthritis n=14). In (B) 93 data points are out of range (arthritis n=44, no arthritis n=49).
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Table 1. Baseline characteristics of the patients visiting the Leiden and Groningen EA RC, separated for patients with and without arthritis. Characteristics of patients that were included in the Leiden and Groningen Early Arthritis Clinic and that had arrived via regular referrals are also presented.

<table>
<thead>
<tr>
<th>EARC Leiden</th>
<th>Regular referrals Leiden</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td><strong>No Arthritis</strong></td>
</tr>
<tr>
<td>n=400</td>
<td>n= 232</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>293 (73.3)</td>
</tr>
<tr>
<td>Age, years, mean±SD</td>
<td>51.3±16.1</td>
</tr>
<tr>
<td>Gradual onset complaints, n (%)</td>
<td>257 (64.3)</td>
</tr>
<tr>
<td>Morning stiffness, minutes</td>
<td>15 (10-60)</td>
</tr>
<tr>
<td>HAQ (0-3)</td>
<td>0.75 (0.25-1.25)</td>
</tr>
<tr>
<td>TJC ‡</td>
<td>8 (4-18)</td>
</tr>
<tr>
<td>SJC, mean±SD</td>
<td>-</td>
</tr>
<tr>
<td>ESR, mm/hour †</td>
<td>-</td>
</tr>
<tr>
<td>ACPA positive, n (%) †</td>
<td>-</td>
</tr>
<tr>
<td>RF, positive, n (%) †</td>
<td>-</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th></th>
<th>EARC Groningen</th>
<th>No Arthritis</th>
<th>Arthritis</th>
<th>Regular referrals Groningen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>133 (62.7)</td>
<td>68 (63.0)</td>
<td>65 (62.5)</td>
<td>92 (62.6)</td>
</tr>
<tr>
<td>Age, years, mean±SD</td>
<td>49.4±16.5</td>
<td>48.1±16.1</td>
<td>50.7±16.9</td>
<td>52.1±16.9</td>
</tr>
<tr>
<td>Gradually onset complaints, n (%)</td>
<td>137 (64.6)</td>
<td>76 (70.4)</td>
<td>61 (58.7)</td>
<td>88 (59.9)</td>
</tr>
<tr>
<td>Morning Stiffness, minutes</td>
<td>30 (10-60)</td>
<td>30 (10-60)</td>
<td>30 (15-90)</td>
<td>15 (0-60)</td>
</tr>
<tr>
<td>HAQ (0-3)</td>
<td>0.63 (0.25-1.13)</td>
<td>0.63 (0.25-1.00)</td>
<td>0.75 (0.38-1.38)</td>
<td>-</td>
</tr>
<tr>
<td>TJC</td>
<td>9 (3-16)</td>
<td>10 (5-18)†</td>
<td>6.5 (2.25-14.75)†</td>
<td>1 (0-5)</td>
</tr>
<tr>
<td>SJC, mean±SD</td>
<td>-</td>
<td>-</td>
<td>3±3</td>
<td>2±4</td>
</tr>
<tr>
<td>ESR, mm/hour †</td>
<td>-</td>
<td>-</td>
<td>14 (7-24)</td>
<td>15 (8-30)</td>
</tr>
<tr>
<td>ACPA positive, n (%)‡</td>
<td>-</td>
<td>-</td>
<td>10 (11.6%)</td>
<td>27 (18.4%)</td>
</tr>
<tr>
<td>RF, positive, n (%)†</td>
<td>-</td>
<td>-</td>
<td>20 (22.2%)</td>
<td>47 (32.0)</td>
</tr>
</tbody>
</table>

Unless otherwise stated values are median (IQR).

† These variables were collected at the first regular outpatient clinic visit and therefore absent for the patients that at the EARC had no arthritis.

‡ The TJC in the EARC is as reported by the patients and the TJC of the patients that arrived via regular referrals is assessed by the rheumatologist.

In the two Leiden and two Groningen data-sets, baseline characteristic between arthritis patients with and without information on the dates of symptom onset or the dates on first GP-visit were not significantly different (data not shown).

EARC, Early Arthritis Recognition Clinic; HAQ, Health Assessment Questionnaire; SJC, Swollen Joint Count; ESR, Erythrocyte Sedimentation Rate; ACPA, Anti-Citrullinated Protein Antibody; RF, Rheumatoid Factor; TJC, Tender Joint Count.
**GP-delay in UA and RA**

The GP-delay of arthritis patients with different diagnoses is depicted in figure 3A. Evaluation of the Leiden EARC patients (n=83) that at baseline were diagnosed with UA or RA revealed a median GP-delay of 2.1 (0.7-8.1) weeks. The median GP-delay of the UA-patients or RA-patients (n=76) that were referred regularly during the same period as the EARC existed was 9.4 (6.0-15.8) weeks, which was significantly longer than that of UA-patients or RA-patients that arrived via the EARC (P<0.001). Our historical data on RA-patients also showed a longer median GP-delay (11.8 weeks). The median GP-delay in the UA-patients or RA-patients identified via the EARC in Groningen (n=44) was similar to that in the Leiden EARC, namely 2.9 (0.5-16.4) weeks.

**Total delay of early arthritis patients**

In all patients screened at the EARC, the median total delay was 14.0 (4.6-76.6) and 16.5 (4.8-60.9) weeks in Leiden and Groningen respectively. Evaluating all arthritis patients, the median total delay in Leiden was 8.6 (3.6-22.3) weeks which was considerably lower than arthritis patients that came via regular referral during the same period as the EARC was running, where the median total delay was 21.0 (9.6-52.1) weeks, p<0.001 (figure 2B). The total delay of 8.6 weeks was also lower than that of the historical data where the median total delay was 13.7 (5.7-28.5) weeks. The median total delay of arthritis patients identified in the Groningen EARC was quite similar (10.6 weeks, IQR 3.1-30.8 weeks) to that of Leiden EARC early arthritis patients (figure 2B) and much lower than that of regular referral patients from Groningen (21.6 weeks IQR 8.1-104.3, p<0.001).

**Total delay in UA and RA**

The total delay per diagnosis is shown in figure 3B. When studying the Leiden EARC patients that were diagnosed with UA or RA at the first regular outpatient clinic visit, the total delay was 7.6 (3.5-23.8) weeks. This was considerably lower than the total delay of UA-patients and RA-patients that were referred by regular routes, which was 19.3 (9.4-40.3) weeks. Our historical data also showed a longer median total delay in RA-patients namely, 18.4 (10.4-35.0) weeks. Together, these results are indicative of a substantial decrease in total delay of UA-patients and RA-patients that were identified via the EARC. UA-patients and RA-patients from the Groningen EARC had a median total delay of 10.4 (3.5-20.4) weeks.

**Proportion of patients seen < 12 weeks after symptom onset**

The proportion of patients that visited the rheumatologist within 12 weeks after symptom onset was evaluated as well. The percentages of all early arthritis patients that were identified via the EARC were 59 and 51 in Leiden and Groningen respectively. In contrast, 32% and 38% respectively of early arthritis patients that came via regular referrals were seen within 12 weeks, and therefore showed lower percentages than the EARC groups (p<0.001 and p=0.074) (See figure 4A-D).
This analysis was repeated among the patients classified with UA or RA that came via the Leiden and Groningen EARC, 65% and 53% respectively arrived <12 weeks after symptom onset. Only Leiden, but not Groningen, UA and RA-patients that arrived via regular referrals were available for comparison, showing a much lower percentage (36%) of patients that was identified <12 weeks’ time (see figure 4E,F). Historically, 31% of RA-patients visited rheumatologists within 12 weeks’ time. Altogether, the percentage of UA-patients and RA-patients that was identified within the first three months after symptom onset has almost doubled when using the EARC.

Figure 3. General practitioner-delay (A) and total delay (B) of the patients screened with arthritis at the Early Arthritis Recognition Clinic (EARC) according to the diagnosis made by the rheumatologists at the first regular outpatient clinic visit.

Legend Figure 3. Patients from the Leiden and Groningen EARC were combined in one figure. Each data point represents a single patient; the black horizontal lines show the median. In (A) three data points are out of range. In (B) 15 data points are out of range. React, reactive arthritis viral and bacterial; Sarc, Sarcoidosis; Cryst, Crystal arthritis; SLE, systemic lupus erythematosus; UA, undifferentiated arthritis; OA, osteoarthritis; RA, rheumatoid arthritis 2010 criteria; PsA/SpA, psoriatic arthritis/spondyloarthritis; Other, Other diagnosis.
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**Figure 4.** Proportion of Leiden and Groningen early arthritis patients (A-D) and Leiden UA and rheumatoid arthritis-patients (E, F) that at first presentation at the rheumatologists had symptoms for less than 12 weeks.

**Legend figure 4.** Black: proportion seen by a rheumatologist < 12 weeks after symptom onset. Grey: proportion seen by a rheumatologist > 12 weeks after symptom onset. The proportion of patients seen within 12 weeks was A: 32%, B: 57%, C: 37%, D: 51%, E:36% and F: 62%.

**DISCUSSION**

Early initiation of treatment of RA is associated with a higher chance of achieving remission and less progressive joint destruction. Early start of treatment requires early identification of arthritis and of RA. A recent study across Europe in RA-patients revealed that the median period between first symptoms and first visit to the rheumatologist is considerable and that the proportion of patients seen within 12 weeks after symptom onset ranged between 8% and 42%.

In our setting, delay in referral by GPs was the main contributor to the total delay. To reduce this delay we initiated an EARC. The present study, which evaluated the efficacy of this screening clinic, revealed that the GP-delay decreased from about eight weeks to about two weeks in arthritis patients. Furthermore, the proportion of patients that was
identified with UA or RA within the first 3 months of the disease has doubled. Based on these results we conclude that the EARC strategy significantly decreases the delay in recognizing arthritis and RA.

Throughout Europe several other strategies were developed to recognize arthritis at an early stage or to increase awareness of arthritis symptoms. For example in Vienna the ‘Rheuma-bus’-initiative was launched and, more recently, an Immediate Access Clinic was established. Elsewhere, triage systems and the effectiveness of education of GPs were evaluated. A difference with some of these initiatives is that the present EARC focuses particularly on decreasing the GP-delay in referring arthritis patients.

This new referral strategy was initiated at two different places that are situated 200 km apart in the Netherlands. Strength of the current study is that the GP-delay and total delay of arthritis patients at both places were comparable.

In order to evaluate the efficacy of the EARC two comparisons were made. Both have drawbacks. The comparison with delay data obtained before the initiation of the EARC is informative. Nevertheless, although the delay durations were stable between 1993 and 2006, differences in delay durations with those of the patients screened at the EARC in 2010 and 2011 may have other reasons than the EARC itself. A limitation of the comparison between EARC arthritis patients and arthritis patients that came via regular referrals is that the motivations of the GP to send to the EARC or to use the regular referral route were not evaluated. In this study referral strategies were not randomized and none of the control groups yielded perfect comparability. Nonetheless, in both control groups the delays observed were longer than those of the arthritis patients identified by the EARC.

Another shortcoming is that we depended on patients’ memory for collecting the dates of symptom onset and of first visits to the GPs. A study in patients with acute heart disease showed a good agreement at the aggregate level between self-reported delay and delay data obtained by structured interviews, suggesting that this way of collecting data is acceptable. Nonetheless, patients with symptoms for a relatively short time period may be more precise in indicating the exact dates than patients that experience symptoms for years.

When evaluating the length of the delay in relation to the diagnoses, it is evident that diseases characterized by an acute severe onset such as sarcoidosis and reactive arthritis had the lowest delay (figure 3), and patients diagnosed with RA, UA, PsA or SpA had the longest delay. This observation is in line with our previous findings.
The EARCs aims to decrease the GP-delay as this is the main contributor to the total delay in the Netherlands. Recent UK studies revealed that patient delay was most the most important factor here. The EARCs did not address the level of delay that is caused by the patients themselves. Hence the applicability of an EARC should be regarded in the context of the local setting.

We did not calculate whether the initiation of an EARC is cost-effective. Given that almost one out of two patients screened had arthritis and that the costs of screening by physical examination are low (5-10 minutes per rheumatologist per patient), it may well be cost effective. Most important is to determine prospectively whether the group of RA-patients identified via the EARC indeed has a better long-term outcome than the group of RA-patients that was identified at our clinic via regular referrals. Longer follow-up of these two groups is therefore required.

Altogether, EARCs were initiated at two different places and the first results of these EARCs consistently showed that this initiative importantly increased the early identification of arthritis and RA.
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REFERENCE LIST


Early identification of rheumatoid arthritis


SUPPLEMENTARY DATA

Supplementary Figure 1.