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## **Patient-physician discordance in global assessment in rheumatoid arthritis: a systematic literature review with metaanalysis**

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## **ABSTRACT (249 words)**

**Objective:** The integration of the patient in therapeutic decision-making is important in the management of rheumatoid arthritis (RA); but the patient opinion regarding disease status may differ from the physician's opinion. The aim of this study was to assess in the published literature the frequency and drivers of patient-physician discordance in global assessment in RA.

**Method:** Systematic literature review by 2 investigators of all papers published up to January 2015 in Medline or EMBASE, reporting discordance in RA. Discordance was defined based on the absolute difference of patient global and physician global assessments (PGA/PhGA) on 0-10cm scales. The frequency of discordance and its predictors were collected in each study. Frequencies of discordance were pooled by metaanalysis using random effect.

**Results:** In all, 12 studies were selected (i.e., 11,879 patients): weighted mean age  $55.1 \pm 13.9$  years, weighted mean disease duration  $10.4 \pm 9.3$  years, 80.7% were women. The value of the difference  $|PGA-PhGA|$  defining discordance varied between  $\geq 0.5$ cm (N=2 studies) to  $\geq 3$ cm (N=5 studies); the weighted mean value was 2.7cm. The pooled percentage of patients with discordance was 43% (95% confidence interval 36%-51%, range: 25%-76%). PGA was usually higher than PhGA. The drivers of PGA were pain and functional incapacity, whereas drivers of PhGA were joint counts and acute phase reactants.

**Conclusion:** Discordance in global assessment was most frequently defined as a difference of 3 points or more; even with such a stringent definition, up to half the patients were found to be discordant. The long-term consequences of this discordance remain to be determined.

Keywords: rheumatoid arthritis, shared decision-making, global assessment, systematic literature review, metaanalysis

### **Significance and Innovations**

- Discordance between patient global assessment (PGA) and physician global assessment (PhGA) was usually defined as a difference of  $\geq 3/10$  points in published rheumatoid arthritis (RA) studies.
- Up to half the patients with RA had a discordant assessment of global activity compared to their physician.
- PGA was usually higher than PhGA and pain was the strongest driver of PGA; pain without inflammation may explain discordance.

## **Introduction**

In the management of chronic diseases, recommendations insist on the need to work in partnership with the patient. In rheumatology in particular, including rheumatoid arthritis (RA), axial spondyloarthritis and psoriatic arthritis, the integration of the patient in therapeutic decision-making is an important aspect of management (1,2). The American College of Rheumatology core set of disease activity measures includes both patient and physician global assessment of disease (respectively PGA and PhGA) (3). These outcomes are usually assessed on 0-10cm scales. However, the patient's opinion regarding disease status may differ from the physician's opinion (4). One way to explore the gap in assessment of disease is to assess disagreements between PGA and PhGA. Patient-physician discordance (i.e. the difference in ratings of global assessment on a 0-10 scale) can lead to patient difficulties regarding treatment decision-making which could potentially negatively affect medical care with poor adherence, impact on the evolution of the disease and added costs (5).

In RA, there is a heterogeneous literature addressing the gap between PGA and PhGA: there is no standardised, consensual level of disagreement between PGA and PhGA to define discordance in global assessment (6). The frequency of discordance appears variable; and demographic and clinical characteristics, which are potential exploratory factors to predict discordance, are unclear.

The aim of this study was to assess in the published literature the frequency and predictors of discordance between patients and physicians in the global assessment of RA, through a systematic literature review and a metaanalysis.

## **Materials and methods**

### Literature search strategy

A systematic review was conducted according to PRISMA guidelines (7). Risk of bias and heterogeneity were assessed with I-squared (I<sup>2</sup>) and funnel plot. The search aimed to identify all published articles and congress abstracts reporting results on patient-physician discordance in global assessment in RA.

A literature search of the Medline and Embase databases, and main rheumatology congress abstracts (up to January 2015, date of the review) was conducted using combinations of the following terms: "rheumatoid arthritis and (discordance or discrepancy) and global assessment". All articles or abstracts (randomized controlled trials, observational studies, cross-sectional or longitudinal studies) published in English or French were retained. The analysis concerned adults; studies in juvenile arthritis were excluded. A hand search of references was also performed on publications selected for full text review to optimize the relevance for our search.

### Data collection

The abstracts were screened by one reader (C.D.); articles concerning patient-physician discordance in global assessment in RA were obtained in full text and the data were extracted independently by 2 investigators (C.D. and A.H.). Any disagreement was resolved by consensus.

The outcomes collected related to patient-physician discordance were i) definition used for discordance, ii) percentage of discordance and iii) drivers of global assessment. PGA and PhGA are usually assessed on 0-10cm scales: visual analog scales or numeric rating scales, where higher results indicate worse status. Frequently used formulations of the PGA questions are "How do you estimate your disease activity today?" or "Considering all the ways that your arthritis affects you, rate how you are doing."

General items were also collected in each article, including the year of publication, country of origin of the data and patients' demographic variables (gender, mean age and disease duration). Clinical characteristics were collected if available: the Disease Activity Score based on 28 joints (DAS28 ESR) (8) and the Health Assessment Questionnaire (HAQ) (9).

### Data analysis

Weighted means were calculated for continuous variables. The frequency of discordance was pooled by Mantel-Haenszel metaanalysis of proportions using random effects. A sensitivity analysis including only published studies was performed for metaanalysis of frequency of discordance. R (version 3.1.1) was used for all statistical analyses.

## **Results**

### Article selection

In all, 66 abstracts or articles were retrieved and assessed for eligibility (Online supplementary Figure S1): 15 abstracts were selected twice (from 2 databases) and 3 publications were reporting on the same population. Among the 48 remaining abstracts, 17 were relevant but in 5 articles no data were available to calculate the frequency of discordance. Hand search did not find any other article. Overall, 7 articles and 5 congress abstracts were included in the final analysis (6,10–20).

### Demographic characteristics

Articles came from different countries (Table 1): one study was international (QUEST-RA (21)), the others came from Austria, USA, Canada, Japan and Brazil. The 12 publications reported on a total of 11,879 patients with RA (of whom 7028 in the large international study (6), QUEST-RA). The weighted mean age was  $55.1 \pm 13.9$  years, 7829 (80.7%) were women and the weighted mean RA duration was  $10.4 \pm 9.3$  years. Early RA patients were analysed in 4 studies (1538 patients) whereas 10,341 patients had established RA. Disease activity was moderate to high (Table 1).

### Definition of discordance

In all, 10 articles (83.3%) reported a cut-off defining discordance with 5 different values (Table 1). The cut-off defining discordance was very heterogeneous varying between  $\geq 0.5$ cm to  $\geq 3$ cm of absolute difference between PGA and PhGA on a 0-10cm visual analog scale or numeric rating scale. The most frequent cut-off was  $\geq 3/10$  (5 studies, i.e. 42% of studies). The other values were:  $\geq 2.5/10$  (N=2),  $\geq 2/10$  (N=2),  $\geq 1/10$  (N=2) and  $\geq 0.5/10$  (N=2). The weighted mean cut-off was 2.7cm and this value was similar for patients with early and established RA. A sensitivity analysis using several cut-offs was done in 4 studies (i.e. 33%) (6,10,13,15).

### Frequency of discordance

By metaanalysis, the percentage of patients with discordance between PGA and PhGA was 43% (95% confidence interval [36%-51%], range: 25%-76%) (Figure 1 and Table 1). Heterogeneity was high,  $I^2$  was 97.2% (Figure 1). The funnel plot indicated an imperfect distribution of the published data (data not shown). This heterogeneity was partly driven by the different cut-offs used;  $I^2$  decreased to 71.8% when analyzing only the studies with a cut-off  $\geq 3/10$  (the most frequent value used).

The sensitivity analysis including only published studies indicated even higher discordance (50%, 95% confidence interval [35%-65%]) but the I<sup>2</sup> was higher (98.8%) (data not shown). There was an inverse correlation between frequency of discordance with more discordant patients when a lower cut-off of |PGA-PhGA| was used to define discordance (Figure 2). A cut-off of  $\geq 0.5/10$  or  $\geq 1/10$  led to around 70% of patients with discordance; a cut-off of  $\geq 2/10$  versus  $\geq 2.5/10$  or  $\geq 3/10$  did not modify the percentage of discordance which was for these cut-offs around 36%.

PGA was usually higher than PhGA: of 4410 patients with discordance, 3486 (79.1%) had a higher PGA than PhGA whereas only 924 (20.9%) had a higher PhGA than PGA. Only one study of 127 patients found more patients in the lower patient-rating group (16).

There were similar rates of discordance in the studies of early or established RA. The percentage of discordance also did not differ significantly between the countries (Table 1).

#### Drivers of global assessment

Of the 12 studies, 8 explored PGA and 6 PhGA. Table 2 shows that the most frequent driver of PGA was pain, significant in 8 studies (100% of studies analysing this driver of PGA). The second predictor of PGA was functional incapacity (assessed through the HAQ). Fatigue was associated with PGA in 2 studies but was not analysed in the other studies. Fibromyalgia was analysed in 2 studies but was not associated with PGA. These results derived from cohorts including patients with long RA duration. However, the 4 studies focusing on newly diagnosed RA patients also found pain as the most frequent driver of PGA (10,16,17,20).

Drivers of PhGA were examination and biology criteria: swollen and tender joint counts and acute phase reactants in 5 studies (Table 2).

#### Drivers of discordance

Some studies specifically analysed drivers of discordance rather than drivers of PGA and/or PhGA. A recent study of 223 RA patients found higher levels of depressive symptoms to be the strongest predictor of discordance (13). However, this is the only study that analysed this variable. Health literacy was predictive of discordance in English-speaking patients in one study, but was not analysed in the other studies (14).



The country of origin of the data did not appear as a relevant factor modifying drivers of global assessment.

## **Discussion**

This systematic literature review brings to light important information on patient-physician discordance in RA. Firstly, discordance was usually defined as a difference of  $\geq 3/10$  points between PGA and PhGA; the weighted mean cut-off used was a difference in global assessment of 2.7 points, which is high. Secondly, and even though such cut-offs were used, nearly half the patients with RA were discordant with the physician indicating there may be a profound difference between how patients and physicians perceive RA. PGA was usually higher than PhGA, i.e., either patients overrated their disease activity, or physicians underrated it. Finally, pain was the most frequent predictive factor of PGA.

This study has strengths and weaknesses. Patient-physician discordance is an important subject and shared decision-making rests on good patient-physician communication (1,22). The systematic character of this review, the double data collection and the analyses of both definitions and frequencies of discordance allow a complete overview of this subject in the literature. We do note that the results may be driven at least partly by one large international study (QUEST-RA, (6)). A weakness of this systematic literature review is that none of the studies explored the full spectrum of the potential explanatory factors of discordance: structural damage, environmental and cultural factors, health expectations, quality of interaction between the patient and the physician. However, the data regarding discordance rates are correct and predictive analyses also bring interesting information. Another limitation of this study was that the inclusion of unpublished studies (with the hypothesis that the quality is inferior) could impact the overall quality of pooled results. However the sensitivity analysis including only published studies had more heterogenous results suggesting that including unpublished studies did not impact the quality of pooled results. Despite the systematic character of this review, the lack of collaboration with a patient research partner and of selection of articles independently by two researchers instead of one are limitations.

There is no standardized way to define discordance. Discordance can be analysed as a continuous value but it is also of course possible to analyse patient-physician discordance using the absolute difference with different cut-offs as a binary value. Using an absolute difference between PGA and PhGA with a cut-off, we can calculate a percentage of patients with discordance whereas continuous values do not allow this. In this systematic literature review most analyses were binarised. The cut-off of  $\geq 3/10$  points of difference was used most frequently. The clinical relevance of assessing patient-physician differences in a binarised way, and of this specific cut-off value, should be discussed. There was an inverse correlation between frequency of discordance and cut-offs used: more patients were discordant when a lower cut-off of  $|PGA-PhGA|$  was used to define discordance which in part reflects the difficulties of pooling results with different cut-offs. On the other hand, this cut-off greatly influences the frequency of discordance: there were twice more patients who were considered discordant when a difference in rating between PGA and PhGA of one point was used ( $\geq 1/10$ ) versus more stringent cut-offs ( $\geq 2/10$  or  $\geq 3/10$ ). Such differences in frequencies of discordance when using different cut-offs suggests few patients had a difference between PGA and PhGA  $\geq 4/10$  points. Our interpretation is that PGA and PhGA are often differing only by 1-2 points in RA. Given the present results and our clinical experience, we suggest a cut-off of  $\geq 3/10$  points for the difference (PGA-PhGA) may be more relevant than a less stringent cut-off, e.g. 1 or 2 points. Indeed, even with a high cut-off such as this, the frequency of discordance remains high.

In the present study, 43% of patients were considered discordant which is very high. This raises questions regarding the symmetry of the PGA and PhGA assessments. Indeed, the questions used for PGA and PhGA are not identical: PGA has several phrasings and may evaluate patient's well being overall or disease activity; whereas PhGA usually evaluates disease activity (23). This could explain at least partly discordance since patient global well-being has been shown to reflect not only the disease status but also psychological distress and comorbidities (23).

In cases of discordance, in most patients (79.1%), PGA was higher than PhGA. PGA was based more heavily on patients' perception of pain, functional incapacity and fatigue (24). In contrast, PhGA were more driven by inflammation; i.e., swollen and

tender joint counts and acute phase reactants. These factors might explain a higher PGA than PhGA. Pain and functional disability are part of the RA Core set (3) and are regularly cited as important by patients with RA (25–27). In established RA, structural damage could explain a high PGA even in the absence of inflammation. However, the percentage of patients with discordance did not decrease even in early disease. Some hypotheses might be that physicians do not detect signs of disease activity (28). Nevertheless, there are objective criteria (joint counts, acute phase reactants) for physicians to assess disease activity. PGA might be interpreted differently by patients and can be influenced by many aspects of the patients' life. Thus, PGA may reflect disease impact, not just the notion of pathological severity implied by disease activity (29). Physicians might not consider the occurrence of a personal life event affecting the PGA. Another cause might be the potential impact of unmeasured cultural factors on disease activity assessment by the patient (30). Fatigue is a frequent aspect of RA, as initially reported by the international scientific organisation Outcome Measures in Rheumatology (OMERACT) (31). The feeling of invisibility and difficulty to describe the experience of fatigue might explain why this is less well taken into consideration by the physician. Furthermore, there might exist a mutual reinforcement of fatigue and pain (32). Only 2 studies looked at associations between discordance and widespread pain syndrome (6,18); this remains an element of the research agenda.

Given the impact of RA on quality of life with an alteration over time, it is possible that there may be a “reference shift” in early disease leading to changes in discordance over the first few years (33,34). However, we found similar percentages of discordance between patients with early or established RA. Longitudinal assessments of discordance were lacking, and furthermore long-term consequences of this discordance remain to be determined.

In conclusion, discordance may have an important impact on shared decision-making. A collaborative approach between the patient, the physician and others health professionals can increase the patient treatment adherence and may improve outcomes (33). Thus, more work is needed on how the discordance between PGA and PhGA impacts clinical outcomes for our patients and whether interventions to reduce discordance would improve outcomes.

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**Table 1** Characteristics of patients with RA in studies reporting on discordance in global assessment



	Number of patients	Women, N (%)	Age, years, mean (SD)	RA duration, years, mean (SD)	Country	DAS 28, mean (SD)	HAQ, mean (SD)	Definition of discordance	Frequency of discordance, N (%)
Kaneko Y, et al 2014 (10)	75 early RA	65 (86)	61 (NA)	0.8 (NA)	Japan	4.5 (NA)	0.7 (NA)	≥0.5/10 ≥1/10 ≥2/10	46 (61.3) 37 (49.3) 27 (36.0)
Furu M, et al 2014 (11)	370 established RA	324 (88)	63 (13)	14 (12)	Japan	3.2 (1.2)	0.8 (0.8)	PGA-PhGA (no cut-off)	PGA>PhGA
Khan NA, et al 2012 (6)	7028 established RA	5609 (80)	55 (14)	11 (9)	International	4.2 (1.8)	1.0 (0.8)	>2/10	2574 (36.6)
Studenic P, et al 2012 (12)	646 established RA	517 (80)	56 (14)	8 (10)	Austria	4.0 (1.4)	0.9 (0.8)	≥0.5/10	491 (76.0)
Barton JL, et al 2010 (13)	223 established RA	197 (88)	53 (14)	NA	USA	4.1 (1.5)	1.3 (0.8)	≥2.5/10	80 (35.9)
Hirsh JM, et al 2010 (14)	110 established RA	87 (79)	53 (12)	13 (10)	USA	4.4 (1.5)	1.0 (0.6)	PGA-PhGA (no cut-off)	-
Nicolau G, et al 2004 (15)	80 established RA	69 (86)	50 (12)	11 (9)	Brazil	3.7 (1.9)	1.4 (0.7)	≥1/10 ≥3/10	57 (71.3) 26 (32.5)
Davis JM, et al 2014 [abstract] (16)	127 early RA	80 (63)	56 (NA)	0.6 (NA)	USA	NA	NA	≥2.5	34 (26.7)

Akhavan P, et al 2014 [abstract] (17)	439 early RA and 737 established RA	NA	58 (NA)	NA	Canada	4.6	NA	≥3	182 (41.5) 309 (42.0)
Diaz-Correa L, et al 2013 [abstract] (18)	213 established RA	188 (88)	57 (14)	11 (10)	USA	NA	NA	>2.5	80 (37.6)
Choi M, et al 2012 [abstract] (19)	897 early RA and 100 established RA	NA	NA	NA	Canada	NA	NA	≥3	324 (36.1) 25 (25.0)
Jones T, et al 2011 [abstract] (20)	834 established RA	693 (83)	48 (NA)	7 (NA)	USA	4.4	NA	≥2	228 (27.3)

Studies are ordered by type (article versus congress abstract) and year of publication

SD: standard deviation, PGA: patient global assessment, PhGA: physician global assessment, DAS28: Disease Activity Score on 28 joints assessment, HAQ: Health Assessment Questionnaire

**Table 2** Drivers of global assessment in 11,879 patients with RA from 12 articles and abstracts reporting on patient-physician discordance

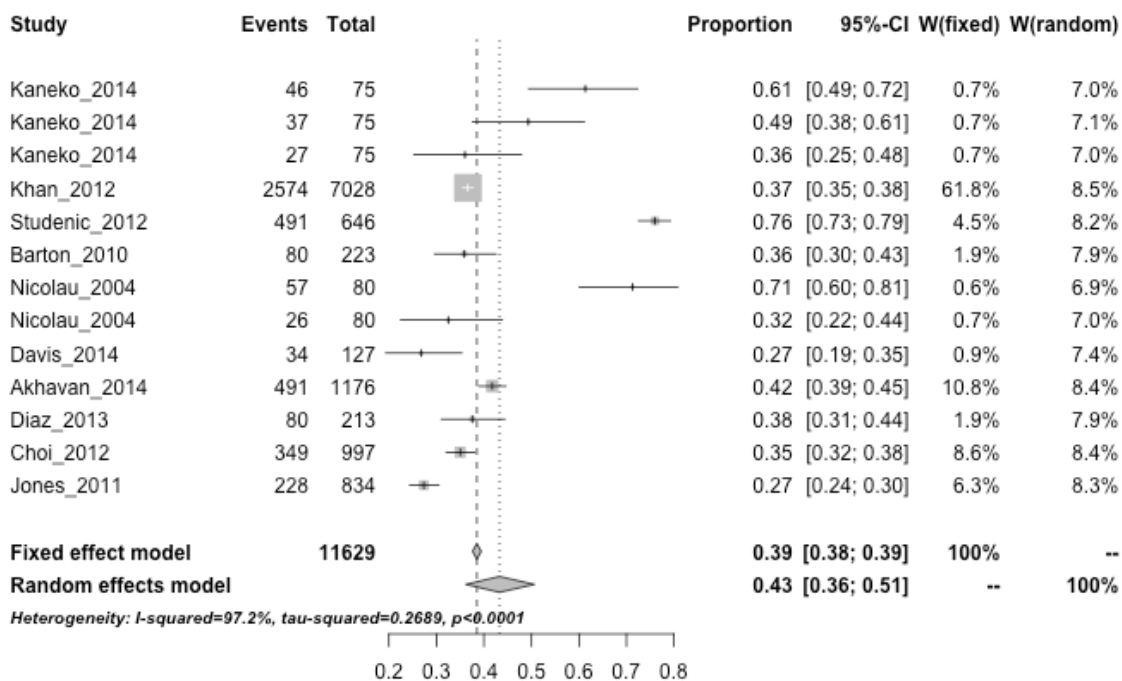
Driver	N studies assessing* [N patients]	N studies finding a positive association# (% of studies) [N patients]
For patient global assessment		
• Pain	8 [9715]	8 (100) [9715]
• Functional incapacity (HAQ)	7 [8539]	6 (86) [8169]
• Fatigue	2 [7155]	2 (100) [7155]
For physician global assessment		
• Swollen/tender joint counts	6 [9427]	6 (100) [9427]
• Acute phase reactants	5 [9300]	5 (100) [9300]
• Pain	6 [9427]	3 (50) [2192]
For discordance		
• Pain	5 [4023]	5 (100) [4023]
• Swollen/tender joint counts	6 [4246]	4 (67) [2415]
• Depressive symptoms	1 [223]	1 (100) [223]
• Health literacy	1 [110]	1 (100) [110]

Only a few articles specifically reported drivers of discordance (last lines).

\* N studies assessing potential exploratory drivers to predict discordance

# N studies finding a positive association with drivers of global assessment (% of studies assessing the driver)

**Figure 1** Forest plot of all articles and abstracts reporting on patient-physician discordance in RA



**Figure 2** Frequency of discordance between PGA and PhGA in 10 studies of RA, according to the cut-off used for the absolute difference  $|PGA-PhGA|$  to define discordance

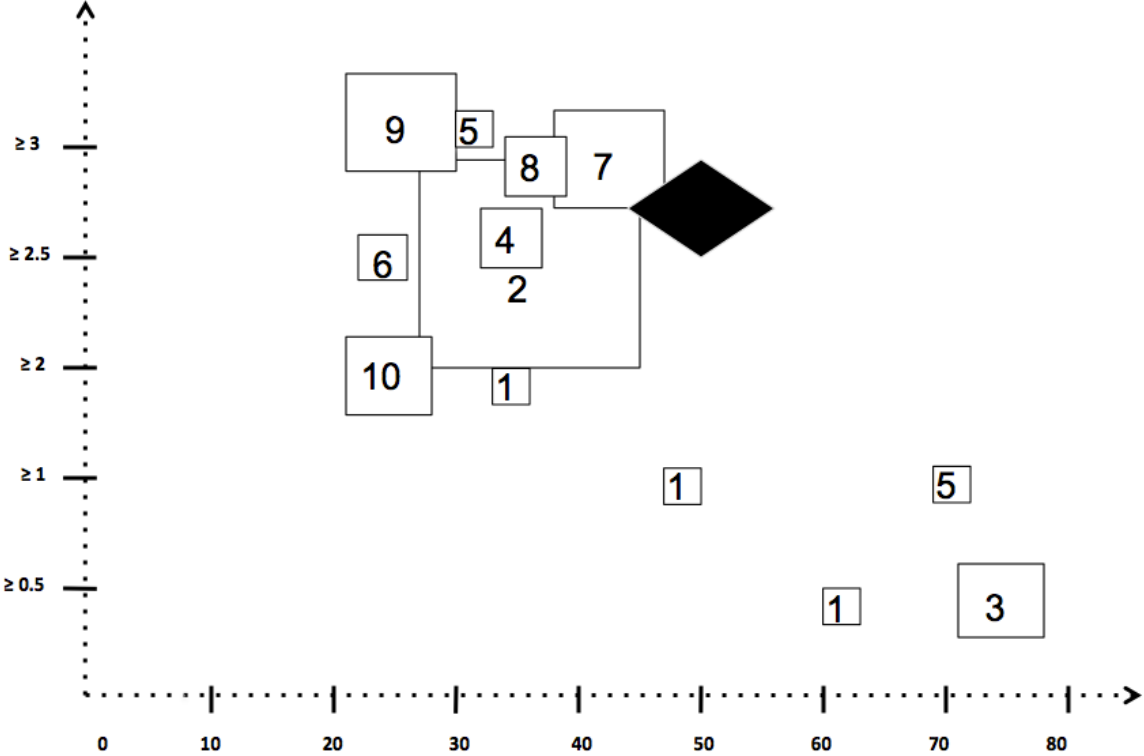


Figure legend

Numbers in the square represent the reference of the study or the congress abstract. The size of the square is a schematic representation of the size of the study. The diamond is a schematic representation of the frequency of discordance by metaanalysis with the weighted mean cut-off.

X axis: frequency of discordance

Y axis: cut-offs of  $|PGA-PhGA|$  defining discordance (0-10)

- (1) Kaneko (10) N= 75, (2) Khan (6) N= 7028, (3) Studenic (12) N= 646,
- (4) Barton (13) N= 223, (5) Nicolau (15) N= 80, (6) Davis (16) N= 127
- (7) Akhavan (17) N= 1176, (8) Diaz-Correa (18) N= 213, (9) Choi (19) N= 997
- (10) Jones (20) N= 834

**Online supplementary Figure S1** Flowchart of selection of published articles and abstracts reporting on patient-physician discordance in RA

