***Rheumatic?* - A Digital Diagnostic Decision Support Tool for Individuals Suspecting Rheumatic Diseases: A Multicenter Validation Study**

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Abstract

Background

Digital diagnostic decision support tools promise to accelerate diagnosis and increase health care efficiency in rheumatology. *Rheumatic?* is an online tool developed by specialists in rheumatology and general medicine together with patients and patient organizations. It calculates a risk score for several rheumatic diseases. In the current pilot study, we retrospectively test *Rheumatic?* for its ability to differentiate symptoms from immune-mediated diseases from other rheumatic and musculoskeletal complaints and disorders in patients visiting rheumatology clinics.

Methods

The performance of *Rheumatic?* was tested using data from 175 patients from three university rheumatology centers covering two different settings:

A. Risk-RA phase setting. Here, we tested whether *Rheumatic?* could predict the development of arthritis in 50 individuals with musculoskeletal complaints and anti-citrullinated protein antibody positivity from the KI (Karolinska Institutet)

B. Early arthritis setting. Here, we tested whether *Rheumatic?* could predict the development of an immune-mediated rheumatic disease in i) EUMC (Erlangen) $n=52$ patients and ii) LUMC (Leiden) $n=73$ patients.

In each setting, we examined the discriminative power of the total score with the Wilcoxon rank test and the area-under-the-receiver-operating-characteristic curve (AUC-ROC). Next, we calculated the test characteristics for these patients at a rheumatology setting passing the first or second threshold for at least one of the rheumatic diseases.

Results

The total test score clearly differentiated between:

A) individuals developing arthritis or not, median 245 versus 163, $P < 0.0001$, AUC-ROC = 75.3

B) patients with an immune-mediated arthritic disease or not, in EUMC median 191 versus 107, $P < 0.0001$, AUC-ROC = 79.0, and LUMC median 262 versus 212, $P < 0.0001$, AUC-ROC = 53.6.

Threshold-1 (advising on seeking primary care doctor) was highly specific in two centers (0.72, 0.87 and 0.23, respectively) and far more sensitive (0.67, 0.61 and 0.67) in KI, EUMC respectively LUMC. Threshold-2 was very specific in all three centers but not very sensitive: specificity of 1.0, 0.96 and 0.91, sensitivity 0.05, 0.07, 0.14 in KI, EUMC respectively LUMC.

Conclusions

Rheumatic? is a web-based patient-centered multilingual diagnostic tool capable of differentiating immune-mediated rheumatic conditions from other musculoskeletal problems. The scoring system might be further optimized, for which we will perform a prospective study.

Background

Despite generally increasing digitalization in rheumatology(1–4), the decision for referral of new patients suspecting rheumatic diseases is mostly analogue with few exceptions and has not changed in the last decades(5, 6).

Diagnostic delays do not seem to improve significantly(7, 8) and often inhibit early, and therefore effective, therapy. Up to 60% of new referrals to rheumatologists end up having no immune-mediated rheumatic disease(9). In contrast to emergency medicine(10), rheumatology has not yet developed objective and transparent triage standards, further complicating patient referral. Incomplete, illegible and not importable paper-based referral forms seem to be outdated and a bottleneck in current clinical care.

Digital diagnostic decision support systems (DDSS) and in particular online self-referral (OSR) systems and symptom checkers (SC) promise to accelerate diagnosis in rheumatic diseases(11–13) and improve health care efficiency. Currently more than 100 SCs exist(14) and are increasingly used by patients. Only a minority of these SCs showed transparent, published, promising evidence before being publicly available(15, 16, 17). The inclusion of clinical experts and patients in the development process has been recommended by various rheumatology societies(18, 19).

Rheumatic? is such a web-based screening tool available in Swedish, English, German and Dutch.(13) It is developed by designers, engineers, clinical experts and patients. This screening tool was designed to capture patients at risk for developing a rheumatic disease. The initial scoring was done by experts in the respective rheumatic diseases included in the screening tool, and needs further validation and improvement. The aim of this pilot study was to test this multilingual, comprehensive DDSS for people suspecting a rheumatic disease and to validate its discriminatory ability in patients with and without immune-mediated rheumatic problems.

Methods

***Rheumatic?* a web-based screening tool**

Rheumatic? is a web-based screening tool to identify individuals with early signs of or at high risk for developing Rheumatoid Arthritis, Ankylosing Spondylitis, Systemic Lupus Erythematosus, Myositis, Systemic Sclerosis, or Sjögren's Syndrome (in this paper called immune-mediated rheumatic diseases) (13). A team of designers, engineers, clinical experts, patients, and at risk individuals worked together to build a test that was both medically correct and effortless to use for an average person. The weights and thresholds for scoring *Rheumatic?* were defined. In short, a first draft of the questions was made, which was then reviewed and adapted in a collaborative workshop with several experts, to make sure the

questions covered the most important symptoms of each diagnosis while still keeping it as short and relevant as possible. In this workshop, a first draft of the scoring was made, by having the experts approximate how significant each question and option was for each diagnosis. These scorings were then implemented as an interactive prototype where different combinations of answers could be tested, and iteratively improved and revised with input from the experts in several meetings during 2018.

The tool was constructed as part of the JPAST project and versions supported by the EU EIT Health program, and exists in Dutch, English, German and Swedish are at the moment accessible for researchers.

Identifying questions and setting thresholds: experienced clinicians provided prognostic questions for rheumatic diseases, based on their clinical and scientific knowledge. In the next step these experts weighted the importance, the sensitivity and the specificity of each question for a specific disease. The weight of the questions was then used to set threshold-1 for any of the diseases, with the advice to visit a general physician and threshold-2 for any disease, with the advice to visit a rheumatologist (13).

Study Design

This pilot study utilized retrospective data collection, where research patient records were used to fill out the questionnaire. In this pilot phase, we aimed to test the ability to differentiate between immune-mediated and other (osteoarthritis (OA) and gout) rheumatic diseases. The retrospective design allowed us to select a sufficient number of patients with different rheumatic diagnoses.

We investigated two clinical settings covering two different stages of disease development. For this we used data from three different clinical centers.

Setting A concerned Risk-RA individuals with anti-citrullinated protein antibody positivity and musculoskeletal complaints (without arthritis) signifying a high risk for future rheumatic diseases.. Here the outcome was the development of arthritis which served as gold standard in the analyses. Setting B concerned patients with early unclassified arthritis without a clear diagnosis. Here the final diagnosis of different rheumatic diseases, fulfilling classification criteria served as the endpoint.

Setting A

Dataset 1 – Karolinska Institutet

We analyzed 50 individuals from Karolinska Risk RA prospective cohort study(20) with at least two years follow up time. The patients were further selected so about half of them developed arthritis during follow up to ensure power to our analysis.

Patients in this cohort are all referred from non-rheumatologist-specialist (in most of the cases primary care doctor) due to suspicions of rheumatic disease, had musculoskeletal complaints and ACPA

positivity without having clinical or ultrasound-based arthritis at the first visit at Karolinska University hospital or Center for Rheumatology in Stockholm, Sweden.

Setting B

Dataset 2 – Erlangen University Medical Centre (EUMC)

Patients referred from a non-rheumatologist-specialist visiting the rheumatology clinic of the Erlangen University Medical Centre (EUMC) with unclassified arthritis? Joint swelling from a prospective cohort study were included. We selected 51 patients with a follow-up of at least one year and a final diagnosis from this cohort, again aiming for a variety of diagnoses and at least 50% patients with non-immune-mediated rheumatic disease (osteoarthritis and gout). Here, we grouped patients by disease and randomly selected patients from the disease groups.

Dataset 3 – Leiden University Medical Centre (LUMC)

Patients visiting the rheumatology clinic of the Leiden University Medical Centre (LUMC) with an initial diagnosis of unclassified arthritis were recruited. These patients with an (not yet classifiable) inflammatory rheumatic disease are included in the Leiden Early Arthritis Clinic(21). After one year of follow-up the final diagnosis was registered. We selected 72 patients from this cohort, aiming for a variety of diagnoses given at the end of the one-year observation period and with and at least 30% patients with osteoarthritis or gout and 70% with the immune-mediated diseases subject to identification with *Rheumatic?*. Here, we grouped patients by disease diagnosed at one year after inclusion and randomly selected patients from the different disease groups with fixed proportions of patients with the different rheumatic diseases.

Statistical Analysis

Rheumatic? Gives a total score, which is built from the individual scores for each of the six diseases. For each disease a participant can pass a first or second threshold, which will inform the participant about the likelihood of having a rheumatic disease. We tested the performance of:

- a. the total score using Wilcoxon rank test and the area-under-the-receiver-operating-curve (AUC-ROC).
- b. the sensitivity and specificity for having an immune-mediated rheumatic disease when passing threshold 1.
- c. the sensitivity and specificity for having an immune-mediated rheumatic disease when passing threshold 2.

All analyses were performed using R. AUC-ROC were calculated using the *pROC* library

Results

Characteristics

By design, the presence of immune-mediated and other rheumatic outcomes were well distributed in each cohort. In KI, 42% of the Risk-RA individuals developed arthritis during the two years follow up. In patients with unclassified arthritis in the EUMC and the LUMC cohorts 55% and 69% were diagnosed with an immune-mediated rheumatic disease after one year of follow-up. Table 1 describes the research individuals and patients in more details.

Table 1

Patient characteristics and outcome in each setting

	Setting A	Setting B	
	KI	EUMC	LUMC
N	50	51	73
Age (median, range)	48 (22-73)	54 (19-82)	59 (19-84)
Sex (%Female)	44 (88)	36 (71)	37 (51)
Non-immune-mediated outcome*	29	23	22
immune-mediated outcome*	21	28	51
<i>Rheumatoid arthritis</i>		5 (10)	8 (11)
<i>Undifferentiated arthritis</i>		4 (8)	10 (14)
<i>RS3PE</i>			4 (5)
<i>Reactive arthritis</i>			7 (10)
<i>Psoriatic arthritis</i>		8 (16)	5 (7)
<i>MCTD or vasculitis</i>		3 (6)	6 (8)
<i>Sarcoid</i>		1 (2)	6 (8)
<i>Paramalignant</i>			5 (7)
<i>Systemic sclerosis</i>		1 (2)	
<i>Spondyloarthropathy</i>		4 (8)	
<i>Systemic Lupus Erythematosus</i>		1 (2)	
<i>Osteoarthritis</i>		23 (45)	17 (23)
<i>Gout</i>		1 (2)	5 (7)
<p>* the immune-mediated outcome was the development of inflammatory arthritis in setting A and the development of an immune-mediated rheumatic disease in setting B. RS3PE = remitting seronegative symmetrical synovitis with pitting edema</p>			

Discriminatory ability of the total score

In each cohort there was a wide variety in scores. Overall, patients who developed an immune-mediated disease after one or two years had a significantly higher *Rheumatic?* score at recruitment compared to those who did not $P < 0.0001$ in all centers (Table 2, Fig. 1).

Table 2
Total *Rheumatic?* score in each setting

	Mean score	Median	Min	Max	P- value *
KI					
All	203	186	7	445	
Arthritis	260	245	101	445	< 0.0001
No arthritis	161	163	7	444	
EUMC					
All	164	134	14	482	
immune-mediated RD	204	191	14	482	< 0.0001
Non immune-mediated RD	115	107	29	235	
LUMC					
All	240	234	80	536	
immune-mediated RD	245	262	80	536	< 0.0001
Non immune-mediated RD	229	212	87	459	
<i>*P-values are calculated using the Wilcoxon rank test</i>					
<i>RD = rheumatic disease</i>					

At KI, the individuals who did not develop arthritis had a lower median score at inclusion as compared with individuals who developed arthritis (163 versus 245, $P < 0.0001$). Similarly, the lower scoring bound was substantially lower in those who did not develop arthritis (7 versus 101). At EUMC, we observed a similar distinct difference in median score between the patients who developed a non-immune-mediated and immune-mediated groups: 107 versus 191, $P < 0.0001$. There was no clear difference in the lower bound of scores (14 and 14), but the upper bound differed highly (235 versus 482). In the LUMC, all patients scored at least 80 points. Again, we found a difference in median score between those who developed an immune-mediated rheumatic disease (imRD) and those who did not, but this difference was smaller than in the other centers (212 versus 262, $P < 0.0001$). Here too, the maximum score differed between the two groups: 459 versus 536.

The overall discriminatory performance, as calculated with the AUC-ROC (95% Confidence Interval), was good in the KI (75.3%, (61.8%-88.8%)) and EUMC data (79.0%, (66.2%-91.8% 95% CI), but less so in the LUMC data (53.6%, (39.2%-67.9%)) (Fig. 2).

Performance of *Rheumatic?* threshold

Though the overall score is informative, the value of *Rheumatic?* is to support patients to seek adequate care when they are at risk of any of the rheumatic diseases. Patients with a low overall score but a high score for one disease, should still be advised to seek medical care.

In setting A, consisting of individuals presenting without arthritis but with ACPA positivity and musculoskeletal complaints, the individuals who developed arthritis passed threshold 1 substantially more often than those who did not develop arthritis (28% versus 16%, Table 3). This difference was less clear, by design, for threshold 2, as in setting A individuals do not have any rheumatic disease, which only a small minority reached (1 patient (2%) and 0 patients(0%). This resulted in a sensitivity and specificity of 67% and 72% for threshold 1, and 5% and 100% for threshold 2.

Table 3
Performance of *Rheumatic?* in each cohorts in identifying immune-mediated rheumatic diseases using the predefined thresholds

	KI		EUMC		LUMC	
	Arthritis	No Arthritis	imRD	No imRD	imRD	No imRD
Not passing threshold 1	7	21	11	20	17	5
Passing threshold 1	14	8	17	3	34	17
sensitivity	67%		61% (41–78%)		67% (52–79%)	
specificity	72%		87% (66–97%)		23% (8–45%)	
Not passing threshold 2	20	29	26	22	44	20
Passing threshold 2	1	0	2	1	7	2
sensitivity	5%		7% (1–24%)		14% (6–25%)	
specificity	100%		96% (78–100%)		91% (71–99%)	
imRD = immune-mediated rheumatic disease, between the brackets is the 95% Confidence Interval						

In setting B, where patients had unclassified arthritis but in a subset this arthritis was caused by a non-immune-mediated disease (gout or osteoarthritis), we observed a similar pattern. Patients who developed a rheumatic disease versus those who did not, passed threshold 1 in 33% versus 6% and 47% versus 23%

of times in EUMC and LUMC, and threshold 2 in 4% versus 2% and 10% versus 3% respectively. This resulted in a sensitivity of 0.61 and 0.67 for threshold 1 and 0.07 and 0.14 for threshold 2 in EUMC and LUMC respectively. The specificity was 0.87 and 0.23 for threshold 1 and 0.96 and 0.91 for threshold 2.

Discussion

Principal Results

We describe a pilot validation study of, to our knowledge, the first multilingual DDSS developed for people suspecting a rheumatic disease. To our knowledge, this is also the first multicenter validation study of a rheumatic DDSS. In our pilot study we tested the performance of *Rheumatic?* in 175 research individuals and patients from three different university centers. We observed a high performance of this online tool in differentiating individuals and patients with immune-mediated rheumatic conditions versus those without, both when using the total score and when applying the currently implemented thresholds. We tested *Rheumatic?* in the setting of individuals with musculoskeletal complaints where only a subset developed arthritis. Here the AUC-ROC was 75%. We furthermore tested the tool in the setting of patients with unclassified arthritis, where a subset had gout or osteoarthritis instead of an immune-mediated rheumatic disease. Here we observed laudable performance with AUC-ROC. These results were less convincing in the final data set of the LUMC, with an AUC-ROC of 54%.

Rheumatic? currently has expert-based thresholds for several rheumatic diseases, where passing threshold 1 for any one of the diseases gives the advice to visit a general doctor. Passing threshold 2 triggers the advice to visit a rheumatologist. Here we observed that threshold 2 is highly specific for immune-mediated condition. However, in our setting it lacked sensitivity by identifying far too few patients with immune-mediated conditions. The sensitivity of threshold 1 was much better, though not optimal, with 0.61 to 0.67. The results of our pilot study suggest that the thresholds might need to be optimized by defining different scores for the threshold, and perhaps reviewing the scoring of the specific questions.

The comparison between the data of the three different centers provides some interesting insights. We used data from existing cohorts, that all had their own approaches for selecting research individuals and patients. We cannot draw hard conclusions about the differences between the inclusion methods as they are applied in different centers. However, the observed differences seem to support the validity of *Rheumatic?* For instance, the higher scores in KI compared to LUMC could be explained by the selection of individuals with ACPA positivity and high risk for rheumatoid arthritis in KI. Similarly, the overall highest scores at the LUMC, as well as the much higher minimum scores there, could be explained by the selection of patients with immune-mediated arthritis. This might also explain the lack of discriminative ability of *Rheumatic?* in the LUMC data. This dataset contains patients for whom the rheumatologist also considered an immune-mediated condition. Both the rheumatologist and *Rheumatic?* use the same questions to come to this conclusion.

Limitations

Our study has several limitations. First, due to the enrichment of non-immune-mediated rheumatic conditions the datasets in Setting B did not reflect the true prevalences of the individual diseases and therefore we cannot calculate the positive and negative predictive values. Secondly, retrospectively entering symptoms (setting B) described by patients introduces a DDSS usage bias. Finally the initial aim of the tool was to identify patients at risk for developing rheumatic diseases. Our datasets contained patients who were already selected by experts for being at risk, excluding those with unspecific signs of arthralgia or other musculoskeletal problems. Nevertheless, *Rheumatic?* was able to further differentiate within this group.

To further optimize the performance we need larger samples sizes than in the current study. Also, we would need to include patients without a rheumatic condition and having patients filling out the questionnaire by their own. An additional way of optimizing the sensitivity is to link the usage of the DDSS tool to genetic and immunological blood testing for specific biomarkers as currently under development in our rheumatology units.

Two recently started studies, a prospective multicenter study and a population-wide study, will further help to ameliorate *Rheumatic?* performance.

Comparison with Prior Work

In 1991, Moens et al. concluded that rheumatology is a suitable domain for computer-assisted diagnosis(11). Despite the elapsed time, such systems are still not part of standard rheumatology care. Alder et al. concluded in a review in 2014 that the validation process of rheumatology DDSS was in general underappreciated and none of the systems seemed to have succeeded in daily practice(12).

Patients and rheumatologists, however, still seem to believe in the positive potential impact of a patient facing Digital Diagnostic Decision Support Systems. A recent study showed that 80% of physicians agreed that an app that could diagnose symptoms of rheumatic diseases in patients will be helpful(22). Furthermore, in a recent survey study 50% of RMD patients stated that they would be interested in using an app for symptom decision support(1).

An RMD DDSS, based on a fuzzy cognitive map technique showed a diagnostic accuracy of 87% in a validation study with 15 vignette cases(22). In a prospective pilot study, 34 patients completed an NHS and WebMD symptom checker. Only 4 out of 21 patients with immune-mediated arthritis were given a first diagnosis of rheumatoid arthritis or psoriatic arthritis(23). People suspecting axial spondyloarthritis (axial SpA), using an online-self-referral were diagnosed in 19.4% with axial SpA(24). This proportion being significantly higher than the assumed 5% prevalence of axial SpA in patients with chronic back pain(25).

Besides patient facing DDSS / symptom checkers, DDSS also represent a great tool for physicians to improve their diagnostic skills. DDSS might be especially attractive for young physicians, due to their limited work experience. McCrea et al showed that using a decision tree lead to an improved accuracy in

medical students diagnosing 10 rheumatology cases (81% compared to 68%). Furthermore, using physician based DDSS could accelerate rare disease diagnosis(26, 27).

Current research suggests that the diagnostic accuracy of DDSS are user dependent(28). The effectiveness of DDSS could also depend on the patient's eHealth literacy, which seems to be limited in RMD patients(1).

A major strength of our study lies in its multicenter approach and large validation sample size compared to previous studies(22, 23). The risk-adverse retrospective validation scenario was deliberately chosen. The majority of currently available symptom checkers seem to skip this validation process, providing little scientific evidence. The DDSS that were evaluated often use patient-vignettes instead of true data (15,27,29). We believe that focusing on improving an international overarching DDSS could boost quality standards in rheumatology by increasing transparency, objectivity and decreasing redundant single-center efforts(13).

Conclusions

By incorporating input from RMD patients, rheumatologists and general practitioners from multiple countries, a multilingual DDSS for people suspecting a rheumatic disease was created. This first validation shows that *Rheumatic?* is capable of differentiating immune-mediated rheumatic conditions from other musculoskeletal problems. Future prospective, patient-lead, and independent studies will provide further validation and amelioration.

Abbreviations

AUC-ROC = area-under-the-receiver-operating-characteristic curve

axial SpA = axial spondyloarthritis

DDSS = Digital diagnostic decision support systems

EUMC = Erlangen University Medical Centre

imRD = immune-mediated rheumatic disease,

KI = Karolinska Institutet

LUMC = Leiden University Medical Centre

OA = osteoarthritis

SC = symptom checkers

RS3PE = remitting seronegative symmetrical synovitis with pitting edema

RD = rheumatic disease

Declarations

Ethics approval and consent to participate

At each site, ethical approval was obtained from the local ethical committees. Patients provided written informed consent when entering a cohort.

Consent for publication

Not applicable

Availability of data and material

The study data and scripts are available from the corresponding author upon reasonable request.

Competing interests

Tor Bruce, Sebastian Evans, Sofia Svanteson and Alexandra Lindfors are or were employees of the companies that developed the Rheumatic? Tool

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Authors' contributions

All authors were involved in the interpretation of the data and drafting the manuscript. RK and TM ran the statistical analyses. LK and AC initiated the development of the tools. RK, JK, AH, AC, DS, AK, GS and TH collected data, TB, SE, MJ, SS, AL, LK, AC, LB and MM developed the multilanguage Rheumatic tool. RK and JK drafted the first version of the manuscript. All gave final approval of the version to be published.

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Figures

Figure 1

Total score in each dataset. Boxplot depicting the differences in total score between those who developed an immune-mediated rheumatic disease (imRD) and those who did not.

Figure 2

(Area under) the receiver operating curve for the total score of Rheumatic?