Running Head: New PsA screening questionnaires

Title: Development and testing of new candidate psoriatic arthritis screening questionnaires combining optimal questions from existing tools

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Abstract (247 words)

Objective: Several questionnaires have been developed to screen for psoriatic arthritis (PsA) but head to head studies have found limitations. This study aimed to develop new questionnaires encompassing the most discriminative questions from existing instruments.

Methods: Data from the CONTEST study, a head to head comparison of three existing questionnaires, were used to identify items with a Youden's index of ≥0.1. These were combined using four approaches: CONTEST- simple additions of questions; CONTESTw- weighting using logistic regression; CONTESTjt- addition of a joint manikin and CONTESTtree- additional questions identified by CART analysis. These candidate questionnaires were tested in independent datasets.

Results: 12 individual questions with a Youden's index of ≥0.1 were identified but 4 of these were excluded due to duplication and redundancy. Weighting for two of these questions, was included in CONTESTw. Receiver operating characteristic (ROC) curve analysis showed that involvement in six joint areas on the manikin was predictive of PsA for inclusion in CONTESTjt. CART analysis identified a further 5 questions for inclusion in CONTESTtree. CONTESTtree was not significant on ROC analysis and discarded. The other three were significant in all datasets, although CONTESTw was slightly inferior to the others in the validation datasets. Potential cut points for referral are discussed.

Conclusion: Of four candidate questionnaires combining existing discriminatory items to identify psoriatic arthritis in people with psoriasis three were found to be significant on ROC

analysis. Testing in independent datasets identifies two questionnaires: CONTEST and CONTESTjt that should be pursued for further prospective testing.

Significance and Innovations

- Existing screening questionnaires for PsA have limitations and head-to-head studies show that they identify different cases of PsA. The new candidate questionnaires in this paper combine the most discriminatory items from existing questionnaires to attempt to create a new, optimal, questionnaire.
- Two candidate questionnaires (CONTEST and CONTESTjt) performed well in both development and validation cohorts. These require further prospective testing to allow recommendation of the best performing tool.

Psoriatic arthritis is a form of inflammatory arthritis associated with skin psoriasis. In the majority of cases, patients present with skin psoriasis prior to developing symptoms of arthritis(1). There is evidence that a significant proportion of psoriasis patients in dermatology clinics(2) and primary care(3) also have unidentified psoriatic arthritis. A variety of screening questionnaires have been developed in an attempt to aid identification of psoriasis patients with possible PsA for subsequent referral. These are typically paper-based questionnaires that are completed by the patients and have a cut-off above which referral is suggested. Most of the questionnaires developed (PAQ(4), PASE(5), PEST(3), ToPAS(6)) have been validated in a variety of independent populations but not compared directly. Recently, the CONTEST study compared three popular screening questionnaires (PASE, PEST and ToPAS) head-to-head in secondary care dermatology clinics at ten sites in the UK(7). The sensitivities and specificities of all three questionnaires were lower than previously found with slightly disappointing AUCs of around 0.6. Interestingly, the prevalence of PsA increased according to the number of positive instruments: the prevalence was 19.1%, 34.0% and 46.8% with one positive, two positive and three positive scores respectively(7). This suggests that a combination of the best performing items from each of the questionnaires may have higher sensitivity and specificity than the individual instruments. The aim of this analysis was to investigate which individual questions from each of the questionnaires performed well and whether a combination of these questions could improve the sensitivity and specificity in identifying PsA.

Methods

Development Cohort (CONTEST)

In the CONTEST study(7), patients with psoriasis but without a diagnosis of PsA were recruited from 10 sites in the UK. Local collaborating dermatologists invited consecutive patients with psoriasis attending dermatology hospital clinics to participate. Patients were excluded if they had an established diagnosis of PsA. Each patient was given an envelope which included a cover letter, study information sheet, the three screening questionnaires (in a random order) and a return envelope. All current versions of the screening questionnaires were used in the study including the updated version 2 of the ToPAS.

Those who scored positively on any of the 3 screening forms were contacted by the local study team and invited to attend for further evaluation by a rheumatologist. Those scoring negative on all three screening forms took no further part in the study. Missing data were not interpolated – only questions answered were scored for the purpose of recording a positive response. Patients were classified as having PsA using the CASPAR criteria.

A total of 938 patients were given the questionnaires and 657 returned them. Of these, 318 were positive for at least one of the questionnaires and were invited to attend for an examination. Of these, 195 attended. There were 47 cases of PsA according to the CASPAR criteria and in addition, 8 cases not fulfilling CASPAR criteria (mostly because a test for rheumatoid factor was not available) but were felt to have a diagnosis of PsA by the examining rheumatologist.

Validation Cohorts

Data from two comparative independent head-to-head studies based in Dublin and Utah were used to test the new proposed questionnaires (2, 8). Both of these studies evaluated some patients with known PsA and some with psoriasis and no known diagnosis of

inflammatory arthritis. Since the latter are the target audience for screening questionnaires, only these cohorts were evaluated. The Dublin data included 100 consecutive psoriasis patients attending dermatology clinics with no known diagnosis of inflammatory arthritis. They completed all three of the questionnaires but no data were available for the joint mannequin. All patients were examined to assess for PsA. A total of 29 patients were diagnosed with PsA according to the CASPAR criteria. In Utah, recruitment letters were mailed to all patients enrolled in the Utah Psoriasis Initiative registry and interested participants attended for a study visit. Additionally, patients with psoriasis attending for routine dermatology or rheumatology appointments were also invited to participate. The Utah data included 269 patients who had completed all three questionnaires and been examined to assess for PsA. Of these, 124 had an established diagnosis of PsA leaving a subset of 145 patients with no previous diagnosis of inflammatory arthritis who were included in this analysis. A total of 80 patients were found to have previously undiagnosed PsA.

Statistical Methods for analysis

Various methods were pursued to develop a new screening questionnaire based on the most discriminatory questions within the three existing questionnaires. For development of the new candidate questionnaires, the diagnosis based on the CASPAR criteria was used to ensure uniformity across centres and cohorts. The questions used to calculate scores for the PEST and ToPAS questionnaires are dichotomous questions, however the questions in the PASE questionnaire use a Likert scale of 1 (strongly disagree) to 5 (strongly agree). In order to compare the questions directly, the PASE questions were transformed into a

dichotomous variable using scores of 1-3 (strongly disagree, disagree or no opinion) as negative but scores of 4 (agree) and 5 (strongly agree) as positive.

All questions from the PASE, ToPAS and PEST questionnaire were investigated individually to look at their sensitivity, specificity and Youden's index and significance using the Chi-squared test. Youden's index (J=sensitivity + specificity – 1) was used as a simple summary measure of misclassification error for the individual items in the questionnaires. This test performs well in such cohorts with low disease incidence and is a useful assessment of both sensitivity and specificity of a diagnostic test. The maximal Youden's index for the individual items was 0.19, so a pragmatic cut off point of 0.1 was used to identify candidate questions.

Method 1: All questions with a Youden's index of ≥0.1 were considered for inclusion in a new questionnaire (CONTEST). As the questions originate from independent questionnaires, it is likely that some questions will ask about the same features (e.g. nail disease or dactylitis) leading to some repetition. To minimise overlap in these situations, the question with the highest discrimination was included.

Method 2: The same methodology was used as per Method 1, except logistic regression was subsequently used to identify any individual questions that were independently predictive of arthritis; odds ratios (OR) from the regression were used for weighting of these questions within the complete questionnaire (CONTESTw).

Method 3: In addition to the standard dichotomous or Likert-scale questions included in the questionnaires, the PEST questionnaire also contains a joint mannequin where patients are asked to tick "joints that have caused you discomfort". ROC analysis was used to identify

whether the number of joints ticked was predictive of PsA and what cut off had the greatest sensitivity and specificity to predict PsA. This was then dichotomised to a score of 0 if less than the cut off were ticked and 1 if that number or more joints were causing discomfort. This question was then added to the questions identified in method 1 (CONTESTjt).

Method 4: All of the individual questions were entered into a classification and regression tree (CART) analysis to develop a classification tree to identify PsA. The CART method selects independent variables that differentiate arthritis but allows different combinations of predictor variables in different subgroups creating a flexible classification system. For example, this potentially allows different questions to be identified for patients with and without enthesitis symptoms. This analysis was used to identify additional questions that could be added to those already identified in method 1 to assess whether they improved differentiation (CONTESTtree).

Comparison of Proposed Questionnaires

All of the questionnaires identified above using methods 1-4 were then assessed using ROC analysis using diagnosis of PsA by CASPAR criteria as the state variable. AUCs were used to compare the proposed questionnaires with each other and also with the original questionnaires from which these were derived. The ROC curves were then used to identify cut points for positivity that could be used to screen for PsA.

Results

Method 1 (CONTEST)

Sensitivities and specificities for all of the questions contained in the PEST, PASE and ToPAS questionnaires are shown in table 1. Using regression analysis, each question was examined

to see if individual questions predicted the likelihood of PsA. In this individual analysis, only 2 questions showed significant differentiation of PsA cases using Fishers exact test: ToPAS 2A "Have you ever noticed any of these changes in your fingernails – pits in the nails?" and PEST 4 "Have you had pain in your heel?". These two questions and a further 10 questions had a Youden score of ≥0.1 and these were considered for inclusion into the first candidate questionnaire (shown in table 2).

There were two questions related to nail pitting (PEST 3 and ToPAS 2A) and as ToPAS 2A performed best, PEST 3 was excluded from further analysis. ToPAS 7A was excluded from subsequent analysis; there appeared to be confusion regarding this question as it was not answered by the majority of patients. ToPAS 9 and 9B were excluded as they ask predominantly about a skin rash, but our proposal for this new questionnaire was that it would be used in patients with established psoriasis. The joint symptoms mentioned in these questions are covered by other questions already included. This left a total of eight questions to form the CONTEST questionnaire with a score of 0-8.

Method 2 (CONTESTw)

Logistic regression (forward stepwise) was used to identify independent predictors of PsA which identified two questions with significant chi-squared results: ToPAS 2A "Have you ever noticed any of these changes in your fingernails – pits in the nails?" and PEST 4 "Have you had pain in your heel?". For ToPAS 2A, the OR was 4.92 (95% CI 1.42, 17.03; p=0.012) and for PEST 4, the OR was 2.23 (95% CI 1.08, 4.61; p=0.031). These odds ratios were applied to the relevant questions to create a weighted version of the 8 item CONTEST questionnaire where ToPAS 2A was weighted as 5, PEST 4 was weighted as 2 and all of the other questions were weighted as 1. Therefore the CONTESTw has a score of 0-13.

Method 3 (CONTESTjt)

ROC analysis identified that the number of positive joints selected on the PEST mannequin alone was predictive of PsA with a AUC of 0.63 (95% CI 0.54, 0.72; p=0.009). Given the proposed use of the questionnaire as a screening tool, a slightly higher sensitivity than specificity was sought. An optimal cut-off of 6 joints or more (sensitivity 0.8, specificity 0.39) was chosen and added to CONTEST as a dichotomised positive/negative score, thus creating the CONTESTjt questionnaire (scoring 0-9).

Method 4 (CONTESTtree)

The CART analysis identified 8 questions and developed a five level tree with 10 terminal nodes. The structure of the classification tree and the prevalence of PsA at each of the terminal nodes are shown in figure 1. As expected, there was some overlap with the questions selected for the CONTEST and CONTESTw questionnaire, although new questions were also included. The first variable selected by the CART analysis was PEST 4 relating to heel pain, which was identified previously as a significant discriminator in both the logistic regression and the individual sensitivity and specificity analysis. Interestingly ToPAS 2A relating to nail pitting was not included in the classification tree. The classification tree included ToPAS 7 and PASE 4 that are already included in the CONTEST questionnaire, but also identified ToPAS questions 6, 7B, 8, 8A and 8B in subsequent nodes. These additional five questions were added to the original 8 CONTEST questions to create the CONTESTtree questionnaire, giving a total score of 0-13.

Comparison of Proposed Questionnaires

All of the questionnaires identified above (CONTEST, CONTESTw, CONTESTjt and CONTESTtree) were then assessed using ROC analysis in the original CONTEST-UK cohort to assess their prediction of PsA (table 3). All of the questionnaires except that derived from the CART analysis reached significance and showed higher AUC than those found in the same data for the original PASE, PEST and ToPAS questionnaires in the development cohort. Given that CONTESTtree did not show a significant AUC, this was not pursued further. ROC analysis in the Dublin and Utah cohort confirmed similar AUC results, although the weighted questionnaire (CONTEST-w) performed slightly inferiorly than the standard questionnaires in these independent cohorts.

Co-ordinates of the ROC curves for the other three questionnaires (CONTEST, CONTEST-w and CONTEST-jt) were then examined using the three cohorts (CONTEST-UK, Dublin and Utah) to assess optimal cut-points for the different candidate questionnaires (table 4). Given that these questionnaires are screening tools, when assessing cut points, the balance of sensitivity and specificity should be in favour of higher sensitivity. Interestingly the optimal cut-points for these candidate questionnaires differed in the three cohorts with higher cut-points appearing optimal in the UK data when compared to both the Dublin and Utah cohorts. Taking into account the results in all of the cohorts, provisional cut offs for the questionnaires are suggested as follows: CONTEST – 4, CONTESTw – 8 and CONTESTjt – 5. However as can be seen in table 4, the optimal cut offs vary in the different cohorts and further validation work is necessary before finalising the cut-offs.

Discussion

The aim of this study was to use all three questionnaires to identify the most helpful questions from each of the instruments and combine them into a new tool. Different

statistical approaches were used both to identify key questions and combine them into new tools. Three of the four proposed questionnaires reached significance in ROC curve testing with higher AUC in the CONTEST data than seen with the original questionnaires. These findings are not altogether surprising as instruments are bound to perform best in the dataset in which they are developed. Further retrospective validation in independent datasets has shown that the weighted questionnaire (CONTESTw) performs less well than CONTEST and CONTESTjt, both of which show reasonable performance in these datasets.

Many screening tools to identify PsA have been developed by independent groups of researchers in recent years. Most have undergone validation, but until recently there has been little research directly comparing questionnaires with the aim of identifying one questionnaire that can be recommended for routine clinical use in the future. There have been three head-to-head comparisons that have shown conflicting results but have all identified problems in identifying PsA(2, 7, 8). In the CONTEST study, the questionnaires identified many cases who had musculoskeletal symptoms due to an alternative diagnosis particularly osteoarthritis or degenerative disease leading to poor specificity(7). In the Dublin study, the specificity was high, but many cases of PsA with predominant axial disease or entheseal disease remained unidentified(2). In the Utah study, both sensitivity and specificity were lower than hoped and the instruments were notably less sensitive in cases with recent onset mild disease(8). All of these studies tested the questionnaires in patients with skin psoriasis but no known inflammatory arthritis, but only positive responders on one or more questionnaire were examined in the UK CONTEST study, whereas all patients were assessed for PsA in the Dublin and Utah cohorts. This key difference in study design results in a slight overestimate of sensitivity and underestimate of specificity in the CONTEST

cohort. This is a limitation for the development of the CONTEST questionnaires as patients who were negative on all three screening questionnaires were not evaluated and therefore their data is not included in these analyses. Although this methodology may have missed some people with PsA, it is likely that their symptoms would be minimal if they are not identified by the questionnaires.

Further prospective validation is now required to identify the optimal questionnaire for PsA screening in both primary and secondary care. The existing studies have already highlighted that the same questionnaires can have conflicting results dependent on the population studied and methodology used. The performance of all questionnaires should ideally be carefully tested in different subsets, including patients with psoriasis recruited from primary care (who should be more representative of the general population) and those recruited from dermatology clinics who are more likely to have severe skin disease.

In summary, this analysis attempts to identify the most discriminatory questions from any of the studied questionnaires, and to combine these into new candidate questionnaires for further validation. The initial evidence from this analysis has created three candidates with marked improvements in AUC compared to the PASE, PEST and ToPAS questionnaires. If replicated in future analyses, any one of the CONTEST questionnaires outlined above could be recommended for future clinical use.

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Table 1 – Sensitivities and specificities of all individual questions in predicting PsA cases

Question	Sensitivity	Specificity	Youdens	Chi-squared	significant
PEST1	0.83	0.25	0.08	1.33	ns
PEST2	0.42	0.61	0.03	0.17	ns
PEST3	0.77	0.33	0.10	1.52	ns
PEST4	0.66	0.53	0.19	4.97	0.03
PEST5	0.60	0.51	0.11	1.70	ns
PASE1	0.68	0.40	0.08	0.87	ns
PASE2	0.81	0.27	0.08	1.27	ns
PASE3	0.65	0.46	0.11	1.83	ns
PASE4	0.57	0.58	0.15	2.84	ns
PASE5	0.47	0.64	0.11	1.63	ns
PASE6	0.34	0.70	0.04	0.25	ns
PASE7	0.57	0.52	0.09	1.19	ns
ToPAS 1	0.97	0.05	0.02	0.09	ns
ToPAS 2A	0.89	0.27	0.16	5.31	0.02
ToPAS 2B	0.71	0.44	0.15	2.87	ns
ToPAS 2D	0.80	0.26	0.06	0.58	ns
ToPAS 3	0.98	0	-0.02	3.25	ns
ToPAS 4	0.96	0	-0.04	6.53	0.01
ToPAS 5	0.96	0.07	0.03	0.49	ns
ToPAS 5B	0.91	0.17	0.08	1.56	ns
ToPAS 6	0.39	0.68	0.07	0.75	ns

ToPAS 7	0.50	0.65	0.15	3.42	ns
ToPAS 7A	0.69	0.41	0.10	0.92	ns
ToPAS 7B	0.43	0.56	-0.01	0.03	ns
ToPAS 8	0.57	0.48	0.05	0.32	ns
ToPAS 8A	0.66	0.24	-0.10	1.49	ns
ToPAS 8B	0.68	0.32	0	0	ns
ToPAS 9	0.89	0.22	0.11	2.79	ns
ToPAS 9B	0.89	0.23	0.12	2.66	ns
ToPAS 10	0.80	0.25	0.05	0.48	ns
ToPAS 12	0.15	0.91	0.06	1.27	ns

Key – grey shading indicates Youden's index ≥0.1, dark grey indicates inclusion in questionnaire

Table 2 – All individual questions with Youden's score of ≥0.1

QUESTION NUMBER	ORIGIN	WORDING	Included in CONTEST questionnaire
PEST 3	PEST	Do your finger nails or toe nails have holes or pits?	NO
PEST 4	PEST	Have you had pain in your heel?	YES
PEST 5	PEST	Have you had a finger or toe that was completely swollen and painful for no apparent reason?	YES
PASE 3	PASE	My back hurts.	YES
PASE 4	PASE	My joints become swollen.	YES
PASE 5	PASE	My joints feel "hot".	YES
ToPAS 2A	ToPAS	Have you ever noticed any of these changes in your fingernails: Pits in the nails as shown in figure 1.	YES
ToPAS 2B	ToPAS	Have you ever noticed any of these changes in your fingernails: Lifting of the nail from the nail bed as shown in figure 2.	YES
ToPAS 7	ToPAS	Have you ever had neck pain lasting at least 3 months that was not injury related?	YES
ToPAS 7A	ToPAS	Was the neck pain accompanied by stiffness?	NO
ToPAS 9	ToPAS	Have you ever had a skin rash on any part of your body at the same time as joint pain, joint-stiffness or swollen red joints?	NO

ToPAS 9B	ToPAS	Do you have skin rash on any part of your body at the same time as joint pain, joint-stiffness or swollen red joints now?	NO

Table 3 – Receiver operator characteristic (ROC) curve analysis of existing and proposed questionnaires in the CONTEST dataset.

Questionnaire	AUC	Lower CI	Upper CI	P value
CONTEST	0.69	0.57	0.81	0.01
CONTESTw	0.74	0.63	0.85	0.001
CONTESTjt	0.70	0.58	0.82	0.006
CONTESTtree	0.59	0.46	0.73	0.20
PEST	0.61	0.52	0.70	0.02
PASE	0.59	0.51	0.68	0.05
ToPAS	0.55	0.46	0.65	0.27

Table 4 – Sensitivities and specificities of all cut offs for the proposed questionnaires in the development (UK) and two validation cohorts (Dublin and Utah)

		UK- CONTEST (n=195)		Dublin (n=100)		Utah (n=145)	
Questionnaire	Cut point	Sens	Spec	Sens	Spec	Sens	Spec
PEST	3	0.766	0.32	0.275	0.98	0.708	0.523
PASE	44	0.745	0.385	0.24	0.94	0.692	0.477
PASE	47					0.585	0.568
TOPAS	8	0.766	0.297	0.41	0.90	0.662	0.386
CONTEST	2	1	0.015	.897	0.324	0.923	0.136
	3	1	0.154	.793	0.789	0.800	0.386
	4	0.86	0.354	.379	0.887	0.615	0.659
	5	0.82	0.523	.207	0.986	0.446	0.818
	6	0.50	0.723	.069	0.986	0.246	0.886
	7	0.27	0.846	.000	0.986	0.123	0.955
	8	0.14	0.938	.000	1.0	0.092	0.955
CONTEST-w	3	1	0.015	.828	0.324	0.877	0.227
	4	1	0.123	.759	0.338	0.785	0.295
	5	1	0.154	.724	0.338	0.723	0.364
	6	1	0.231	.690	0.380	0.677	0.409
	7	0.96	0.323	.655	0.789	0.615	0.5
	8	0.86	0.477	.448	0.887	0.523	0.659

	9	0.82	0.538	.310	0.944	0.400	0.773
	10	0.77	0.662	.069	0.986	0.277	0.909
	11	0.36	0.815	.034	0.986	0.185	0.932
	12	0.27	0.892	.000	0.986	0.123	0.955
CONTEST-jt	3	1	0.108	n/a	n/a	0.862	0.205
	4	0.96	0.246	n/a	n/a	0.754	0.500
	5	0.86	0.369	n/a	n/a	0.569	0.705
	6	0.82	0.615	n/a	n/a	0.400	0.818
	7	0.46	0.723	n/a	n/a	0.246	0.886
	8	0.27	0.846	n/a	n/a	0.123	0.955
	9	0.14	0.938	n/a	n/a	0.077	0.955

Figure 1 – Classification and regression tree (CART) analysis to identify PsA cases