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## Optimal search strategies for identifying moderators and predictors of treatment effects in PubMed

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### Abstract

**Background:** Treatment effects differ across patients. To guide selection of treatments for patients, it is essential to acknowledge these differences and identify moderators or predictors. Our aim was to generate optimal search strategies (commonly known as filters) for PubMed to retrieve papers identifying moderators and predictors of treatment effects.

**Methods:** Six journals were hand-searched for articles on moderators or predictors. Selected articles were randomly allocated to a development and validation set. Search terms were extracted from the development set and tested for their performance. Search filters were created from combinations of these terms and tested in the validation set.

**Results:** Of 4407 articles, 198 were considered to be relevant. The most sensitive filter in the development set ‘(“Epidemiologic Methods” [MeSH] OR assign\* OR control\*[tiab] OR trial\*[tiab]) AND therapy\*[sh]’ yielded in the validation set a sensitivity of 89% [88%–90%] and a specificity of 80% [79%–82%].

**Conclusions:** The search filters created in this study can help to efficiently retrieve evidence on moderators and predictors of treatment effect. Testing of the filters in multiple domains should reveal robustness across disciplines. These filters can facilitate the retrieval of evidence on moderators and predictors of treatment effects, helping the implementation of stratified or personalised health care.

**Keywords:** evidence-based medicine (EBM); information retrieval; PubMed; search strategies

#### Key messages

- The potential of a treatment to be clinically effective can be improved if factors that predict whether or how well a treatment works, predictors and moderators, are included in clinical decision making.
- Optimal search strategies (commonly known as filters) are developed and tested that can retrieve up to 90% of the articles describing predictors and moderators of treatment effects.
- Information on predictors and moderators is necessary to facilitate research on stratified or personalised health care.

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## Background

It is increasingly recognised that patients respond to treatments in different ways (Kravitz, Duan & Braslow, 2004) and that treatments that have been demonstrated to be sufficiently safe on average may still produce serious side-effects in some patients (Bast & Hortobagyi, 2004; Evans & Relling, 2004).

The full potential of a treatment is more likely to be realised if it is targeted according to the biological or risk characteristics shared by subgroups of patients. Therefore, those developing clinical guidelines or making individual patient treatment decisions need to search the medical literature for studies providing information on the effect of patient characteristics on treatment effects. Factors that predict whether a treatment works or not are known as 'predictors'; factors that influence how well a treatment works compared to other options (usually measured by an interaction term) are labelled 'moderators' (Baron & Kenny, 1986; Kraemer, Wilson, Fairburn & Agras, 2002).

Search strategies (commonly known as filters) can facilitate searches for moderators and predictors. They can help researchers to find relevant literature more quickly and easily by reducing the number of articles that a researcher needs to review or allowing a busy clinician to identify a more relevant set of articles within a fixed amount of time (Shariff et al., 2012). Existing search filters have been mainly developed to efficiently retrieve high quality literature on aetiology, diagnosis, prognosis and therapy (Chatterley & Dennett, 2012; Hoogendam, de Vries Robbe, Stalenhoef & Overbeke, 2009; Huang et al., 2016; McKibbon, Wilczynski, Haynes & Team, 2009). One set of filters, the PubMed Clinical Query filters, has been developed to find literature on prognosis, treatment or clinical prediction. This original set of filters can be used to retrieve articles concerning diagnosis or disease staging, study design/methodology, clinical prediction (i.e. prognosis, independent of treatment), outcome measures (including patient reported outcomes and quality of life) or treatment effects in general. However, these pre-existing filters focus on studies investigating a

homogeneous population, or an 'average' patient, and not specifically on moderators and predictors.

### Objectives

The aim of this study was to create search filters to aid in the retrieval of literature on moderators or predictors of treatment effect.

### Methods

For the development and validation of the search filters for PubMed, two steps were taken: (1) a comprehensive set of search terms and combinations of terms were extracted from a set of manually selected relevant papers; and (2) the retrieval performance of these combinations of terms was tested. The methods used followed accepted good practice in search filter creation (Jenkins, 2004; White, Glanville, Lefebvre & Sheldon, 2001).

#### Creation of a set of relevant papers (reference set)

First, we constructed a set of relevant papers by hand searching journals for papers concerning moderators or predictors of treatment effects (containing predictor or moderator analysis as primary or secondary outcome). As an exemplar domain, we selected the field of rheumatology, where personalised health care is becoming increasingly important (Burgos, Danila, Kelley, Hughes & Bridges, 2009; Gibson et al., 2012). Four journals (Annals of the rheumatic diseases, Arthritis care & research, Arthritis research & therapy, and Arthritis and rheumatism) were selected according to their ranking, based on the 5-year Impact Factor in the rheumatology category (Institute of Scientific Information Journal Citation Reports), and supplemented with two high impact general clinical journals (the Lancet and the New England Journal of Medicine).

As a first round of screening, all articles published in these journals in the year 2011 were manually screened in PubMed by title and abstract and classified as possibly

concerning research on moderators or predictors of treatment effects. Any article describing an intervention which either describes in the abstract that moderator, predictor or subgroup analyses were performed, or that gives a strong indication that such factors are investigated, was selected for review. This could include not only RCTs but also any intervention study mentioning regression or subgroup analysis. The year 2011 was selected to allow proper MeSH-term linkage. The following inclusion criteria were used: clinical trials phase III, randomised controlled trials, systematic reviews, meta-analyses, guidelines and/or studies reporting on moderators, predictors, biomarkers or genetic factors related to treatment outcomes. Studies performing safety analysis were also included.

Case reports, comments, editorials, clinical trials phase I and II news and in vitro or animal studies were excluded, as well as studies reporting on predictors of prognosis or diagnosis. Although we used rheumatology as an exemplar domain, we included non-rheumatology related papers as well to increase generalisability of findings outside the field of rheumatology. Articles were restricted to the English language. The first screening was performed by two authors independently (WK and CL or MT and CL); if at least one reviewer considered the article to be potentially relevant, it was included for subsequent full-text examination.

Full texts of the articles selected during the first round of screening were retrieved and subjected to a second round of screening. For inclusion, articles had to mention at least one variable that influenced a treatment outcome, for example as interaction term in a model or stratification variable. Articles were included regardless of study quality, evidence level or direction or size of effect. Each full-text article was independently screened by two authors (WK and CL or MT and CL). A third author (WK, MT, RvH or GJvdW) was consulted if the authors were unsure or no agreement was achieved. The final set of articles was designated as a 'reference set' and used to generate search terms and determine retrieval performance.

### Search terms

The entire set of articles (both relevant and irrelevant) was randomly divided into a development set and a validation set. The development set was used to create the search filters, and the validation set was used to test the search filters. The reference papers in the development set were submitted to PubReMiner to generate a list of all keywords (including truncated keywords to accommodate variations in grammatical form) and MeSH terms related to these articles. PubReMiner is an online tool that creates frequency tables of various properties of submitted queries (Cunningham et al., 1998). Three authors (WK, MT and RvH) filtered out common general terms (e.g. 'method', 'conclusion' and 'objective'), which lack discriminatory power, as well as disease-specific terms related to diagnoses, treatment procedures or outcomes (excluding only if there was a unanimous decision). This evaluation was performed on the meaning of the terms, not the amount of studies they did or did not cover. The remaining keywords and MeSH terms were selected for testing. Each keyword was included with and without specified search fields (text word [tw], title or abstract [tiab], title [ti], MeSH Major Topic [majr], MeSH Subheadings [sh] or MeSH Terms [mh]).

### Testing search filters

The retrieval performance of each search filter (consisting of a single term or combination of search terms) was determined using four accepted measures. The sensitivity (Se), specificity (Sp), accuracy (Ac) and number needed to read (NNR) were calculated according to the formulas listed in Table 1.

Table 1 - Formulas for calculating the sensitivity, specificity and number needed to read

Sensitivity:  $A/(A + C)$ ; specificity:  $D/(B + D)$ ; accuracy:  $(A + D)/(A + B + C + D)$ ; number needed to read:  $1/[A/(A + B)]$ .

	Relevant	Not relevant	Total
Identified	A (true positives, correct inclusion)	B (false positives, incorrect inclusion)	Total identified
Not identified	C (false negatives, incorrect exclusion)	D (true negatives, correct exclusion)	Total not identified
Total	A + C (total relevant hits)	B + D (total not relevant hits)	A + B + C + D (total database)



Sensitivity, in this context, is a measure of the proportion of relevant articles retrieved from the reference set. Specificity is a measure for the nonretrieval of non-relevant citations (McKibbon et al., 2009). Accuracy is defined as the proportion of articles correctly retrieved by the search filter (Haynes, McKibbon, Wilczynski, Walter & Werre, 2005). The number needed to read is defined as the total number of articles to be screened to retrieve one relevant article (Bachmann, Coray, Estermann & Ter Riet, 2002). It is the inverse of 'precision', but easier to interpret for those less familiar with the term.

All terms were tested individually, and those with a Se <25% and Sp <75% were excluded from further analysis. Our methods resembled those used by Haynes, Wilczynski, McKibbon, Walker and Sinclair (1994) and sought to exclude keywords with high Se but unusably low Sp or vice versa. Where similar keywords with different search fields had the same Se and Sp, we excluded the most restrictive term (e.g. from treat\* [tiab] and treat\* [tw], the first was excluded in case of equal Sp and Se). To improve face validity, some specific terms (linked with moderators, predictors or their analysis) were included in the subsequent step irrespective of their performance as a single term. This is not expected to do any harm, as the creation process would filter out these terms if they were not performing well.

To provide an indication of the accuracy of the sensitivity and specificity, confidence intervals are given using the formulas:  $se \pm 1.96 \times \sqrt{\frac{se(1-se)}{n}}$  and  $sp \pm 1.96 \times \sqrt{\frac{sp(1-sp)}{n}}$ , where sp = specific ( $0 < n < 1$ ), se = sensitivity ( $0 < n < 1$ ), and n is the total number of papers in the set.

In a second step, multi-term search filters were tested. To improve face validity of the search filters, the search terms were divided into terms related to treatment outcome (T-term) (e.g. 'outcome', 'treatment') and terms related to moderators/predictors or methodology (M-term) in the broader sense (e.g. 'randomised', 'trial'). Classification was performed by three authors

(MT, WK and RvH) using majority rule. Some terms were classified as neutral (M- and T-term) because they could not be classified as either of these two. An initial set of multi-term search filters was created by combining one T-term and one M-term using a Boolean 'AND' operator. Combinations with a Se <75%, a Sp <50% or an Ac <75% were removed. The remaining combinations were combined one by one with the other M-terms and T-terms using an 'OR' operator with the existing M-terms or T-terms in the filter (i.e. '(T-term1 OR T-term2) AND (M-term1 OR M-term2)'). If the performance measures of this combination improved (with Se, Sp and Ac remaining at  $\geq 75\%$ ,  $\geq 50\%$  and  $\geq 75\%$ , respectively), the extra term was considered to offer additional value. In a computational algorithm, written in C++, additional search terms were tested until no further improvement could be made. Optimal combinations of search terms per filter were generated for each performance measure separately.

The performance of the search filters was determined by applying the search filters to the validation set to obtain the required measures.

#### Sensitivity analysis

To check for generalisability across journals from a specific domain (rheumatology) and general clinical journals, we compared the performance of the search filters within the rheumatology journals and the general clinical journals separately.

#### Results

##### Creation of a set of relevant papers (reference set)

A total of 4407 articles were selected for hand searching; the search string is presented in Appendix A. In total, 198 papers were classified as papers providing information on moderators of predictors of treatment effect (see Appendix B). An overview of the screening process is presented in Figure 1. Table 2 shows the number of papers in the development and validation set per journal.

## Search terms

Submitting the 97 papers that were considered relevant to PubReMiner yielded 1253 MeSH terms and 1231 keywords. Each keyword was combined with six different search fields ([tw], [tiab], [ti], [majr], [sh] and [mh]) or used without any field delimiters resulting in a total of 9870 single-term ( $7 \times 1231 + 1253$ ) searches to be performed in PubMed. Among these, 314 terms resulted in a Se  $\geq 25\%$  and a Sp  $\geq 75\%$ . Of these 314 terms, 121 terms were removed as they were too disease-specific or too general (Appendix C). A list of items (fixed terms) which were forced into the algorithm to improve face validity is also displayed in Appendix C. The distribution of the remaining 193 terms into M-terms, T-terms or neutral terms is shown in Appendix D.

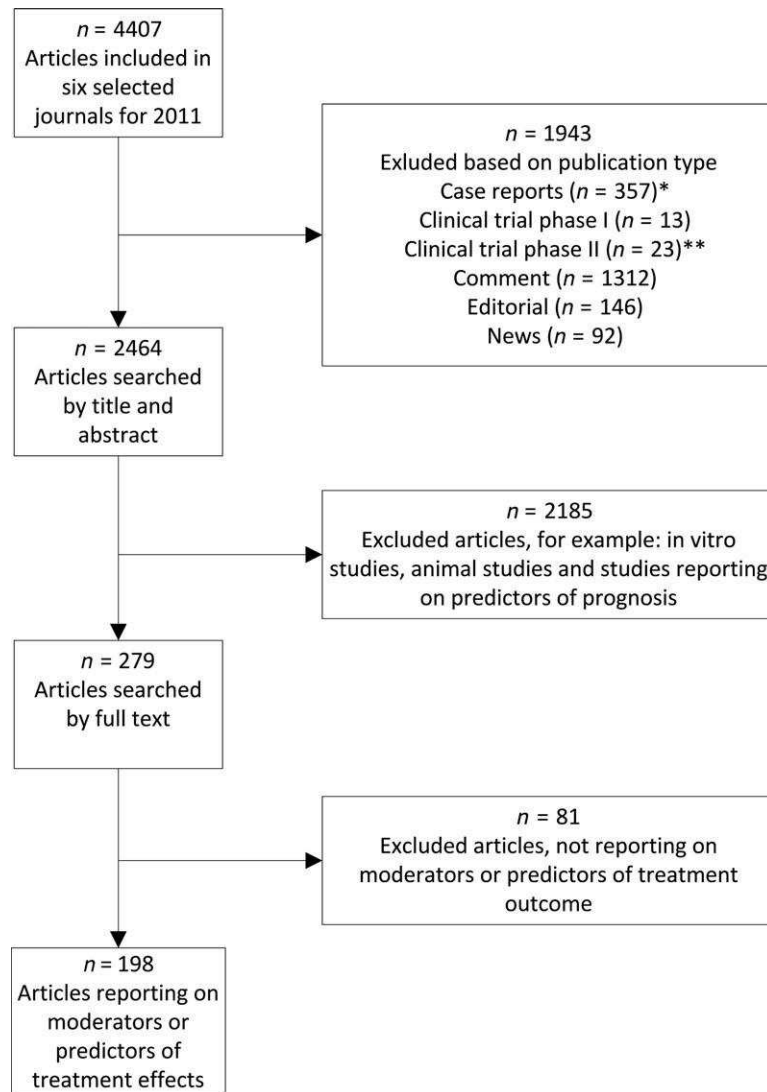


Figure 1 Manual search for relevant papers. \*One paper reporting on a case series and cohort study was not excluded, because none of the index patients were part of the cohort (Korswagen et al.). \*\*One paper was marked in PubMed as a clinical trial, Phase II. However, this paper reported a randomised controlled phase III study and was therefore not excluded based on publication type (Tak et al.)

## Testing search filters

Table 3 shows the best single-term filters, and Table 4 shows the best multi-term filters optimised for Se, Sp, Ac and NNR separately.

When search terms from the development set were applied to the validation set, a decrease in sensitivity (ca. 10%) was observed, but not in specificity. Accuracy decreased by ca. 1%, and NNR increased by ca. 0.5. (Table 4, rightmost columns). The most sensitive filter with the highest Sp ('Epidemiologic Methods' [mesh] OR assign\* OR control\*[tiab] OR trial\*[tiab]) AND therapy\*[sh]) had a Se of 89% and Sp of 80%, and on average, 5.6 papers need to be screened in order to retrieve one relevant paper. The combination (group\*[tw] AND therapy\*) reduces the NNR to 2.8 and increases Sp by about 15%, at the cost of 30% loss in Se.

Table 2 Number of papers in the development set, the validation set and total number of papers considered relevant in the hand search per journal and in total

	Development set (relevant papers)	Validation set (relevant papers)	Total (relevant papers)
Annals of the rheumatic diseases	235 (16)	205 (14)	440 (30)
Arthritis care and research	133 (4)	145 (8)	278 (12)
Arthritis research and therapy	158 (4)	156 (4)	314 (8)
Arthritis and rheumatism	255 (10)	271 (12)	526 (22)
Lancet	714 (28)	738 (27)	1452 (55)
The New England Journal of Medicine	723 (35)	674 (36)	1397 (71)
Total	2218 (97)	2189 (101)	4407 (198)

Table 3 Single-term filters with the best sensitivity, best specificity, best accuracy and the lowest number needed to read for detecting papers reporting on moderators or predictors of treatment effects

Search term	Se (%) [95% CI]	Sp (%) [95% CI]	Ac (%)	NNR
Best				
sensitivity <sup>†</sup>				
treat*	95.9 [95.0–96.7]	79.5 [77.9–81.2]	80.3	5.67
trial*	86.6 [85.2–88.0]	88.3 [87.0–89.6]	88.2	3.95
control*	80.4 [78.8–82.1]	91.5 [90.4–92.7]	91.0	3.31
Best specificity <sup>†</sup>				
intent*[tiab]	29.9 [28–31.8]	98.9 [98.4–99.3]	95.9	1.83
registered	29.9 [28–31.8]	98.8 [98.4–99.3]	95.8	1.86
randomise*[ti]	28.9 [27–30.8]	98.8 [98.4–99.3]	95.8	1.89
Best accuracy <sup>†</sup>				
intent*[tiab]	29.9 [28–31.8]	98.9 [98.4–99.3]	95.9	1.83
registered	29.9 [28–31.8]	98.8 [98.4–99.3]	95.8	1.86
randomise*[ti]	28.9 [27–30.8]	98.8 [98.4–99.3]	95.8	1.89
Lowest NNR <sup>†</sup>				
intent*[tiab]	29.9 [28–31.8]	98.9 [98.4–99.3]	95.9	1.83

### Sensitivity analysis

When the validation set was restricted to the four rheumatology journals, performance measures degraded slightly. In the filters optimised for Se, the average Se dropped from 91% to 78%. In the filters optimised for Sp, the average Sp dropped from 95% to 92%. Ac dropped from 93% to 90% in the Ac-optimised filters, and NNR rose from 2.9 to 5.1 in the NNR-optimised filters. When the validation set was restricted to the two core clinical journals, the performance measures increased; average Se rose to 98%, Sp rose to 96%, Ac rose to 95% and NNR dropped to 2.2.

### Discussion

To our knowledge, this study is the first to report search filters for the retrieval of articles specifically on moderators or predictors of treatment effects. The most sensitive filter is appropriate if comprehensiveness is sought, at the expense of efficiency. If efficiency is more important, a more specific but less sensitive filter is appropriate, in particular the combination (group\*[tw] AND therapy\*). For retrieval of more recent articles which are not yet indexed, we suggest using a filter without either MeSH headings or subheadings.

**Table 4** Combinations of search terms with the best sensitivity, best specificity and lowest NNR for detecting articles reporting on moderators or predictors of treatment outcome

Search filter	Development set				Validation set			
	Se (%) [95% CI]	Sp (%) [95% CI]	Ac (%)	NNR	Se (%) [95% CI]	Sp (%) [95% CI]	Ac (%)	NNR
Optimal sensitivity <sup>†</sup> (‘Epidemiologic Methods’ [mesh] OR assign* OR control*[tiab] OR trial*[tiab]) AND therapy[sh]	100 [100–100]	79.4 [77.8–81.1]	80.3	5.49	89.1 [87.8–90.4]	80.2 [78.6–81.9]	80.6	5.59
(‘Epidemiologic Methods’ [mesh] OR assign* OR control*[tiab]) AND (therapy[sh] OR primary*[tiab])	100 [100–100]	79.1 [77.4–80.8]	80.0	5.57	91.1 [89.9–92.3]	79.3 [77.6 – 81.0]	79.8	5.71
(‘Epidemiologic Methods’ [mesh] OR analys* OR predict* OR trial*[tiab]) AND therapy[sh]	100 [100–100]	78.5 [76.8–80.3]	79.5	5.69	92.1 [90.9–93.2]	79.9 [78.3–81.6]	80.5	5.51
Optimal specificity <sup>†</sup> group*[tw] AND therapy* randomi* AND treat* group*[tw] AND treat*[tw]	75.3 [73.5–77.1] 78.4 [76.6–80.1] 77.3 [75.6–79.1]	94.8 [93.9–95.7] 94.6 [93.6–95.5] 94.5 [93.6–95.5]	94.0 93.9 93.8	2.51 2.51 2.55	58.4 [56.4–60.5] 61.4 [59.3–63.4] 65.3 [63.4–67.3]	94.9 [94.0–95.8] 94.6 [93.7–95.6] 94.6 [93.7–95.6]	93.2 93.1 93.3	2.81 2.81 2.70
Optimal accuracy <sup>†</sup> group*[tw] AND therapy* (randomi* OR hazard*) AND treat* randomi* AND treat*	75.3 [73.5–77.1] 79.4 [77.7–81.1] 78.4 [76.6–80.1]	94.8 [93.9–95.7] 94.6 [93.6–95.5] 94.6 [93.6–95.5]	94.0 93.9 93.9	2.51 2.49 2.51	58.4 [56.4–60.5] 66.3 [64.4–68.3] 61.4 [59.3–63.4]	94.9 [94.0–95.8] 94.3 [93.3–95.3] 94.6 [93.7–95.6]	93.2 93.0 93.1	2.81 2.78 2.81
Optimal NNR <sup>†</sup> (randomi* OR hazard*) AND treat* (randomi* OR multivariate) AND treat* randomi* AND (treat* OR death*)	79.4 [77.7–81.1] 79.4 [77.7–81.1] 79.4 [77.7–81.1]	94.6 [93.6–95.5] 94.5 [93.6–95.5] 94.5 [93.6–95.5]	93.9 93.9 93.9	2.49 2.51 2.51	66.3 [64.4–68.3] 66.3 [64.4–68.3] 64.4 [62.4–66.4]	94.3 [93.3–95.3] 94.1 [93.1–95.1] 94.4 [93.5–95.4]	93.0 92.8 93.1	2.78 2.85 2.78

Se: sensitivity, Sp: specificity, Ac: accuracy, NNR: number needed to read, [tw]: text word field, [sh]: MeSH subheading field, [tiab]: title or abstract field, [mesh]: MeSH term field. Asterisks in the search terms signify search term truncations, e.g. treat\* can be treatment or treating.

<sup>†</sup>Keeping sensitivity >75%, specificity >50% and accuracy >75%.



In the absence of other search filters for finding literature on moderators or predictors of treatment effects, we can compare the efficiency of the resulting filters with those of established search filters (e.g. Haynes et al., 1994; Wilczynski, Walker, McKibbin & Haynes, 1993). These search filters are used to retrieve aetiology, prognosis, diagnosis or treatment related studies, and target a variety of study types with no specific subject, similar to our filters. The methods of development and validation used by these authors are comparable to our own. As in these studies, our study revealed many combinations of keywords reaching >95% Se or Sp. The results from our study showed an optimal NNR for multiterm filters between 2.5 and 5.7, comparable to those reached by Haynes et al. (reaching an NNR of 1.7–4.8, calculated from table 7 in Ref. (Haynes et al., 1994)). Because our filters will also retrieve relevant information from non-RCTs, they appear to have added value to the PubMed Clinical Queries (PCQ) filter for therapy. If these PCQ filters (broad filters) are applied to our validation set, they yield a slightly higher Se (94%) at the cost of a lower Sp (64%) and higher NNR (9.0), where our filters reached 89% Se, 80% Sp and NNR of 5.6. The differences between this filter and our filters can be explained by the fact that the PCQ filters are more generally focussed on treatment effects, which results in a broader set of articles returned often excluding moderators or predictors, hence the higher Se and lower Sp. The Sp optimised PCQ filters (narrow filters) perform similar to our filters at a Sp of 95% with a Se of 64% and only slightly higher NNRs (3.0 versus our 2.8). The fact that our filters and the PCQ filters optimised for Sp perform similarly can be explained by the fact that both aim to select articles on treatment effectiveness. Although in the validation set the differences may be small, our filters do provide added benefit over the PCQ filters if one is specifically interested in moderators or predictors of treatment effects due to their higher specificity, as is evident from the lower NNRs.

The strength of this study is that we tested the retrieval performance of a wide range of candidate search terms (keywords and MeSH terms). Furthermore, combining these terms using an algorithm allowed us to test well over a million different

combinations. The distinction in keyword types (M- and T-terms, respectively) allowed a predefined place for an AND operator within the search filters, a satisfactory alternative to testing search filters with all possible combinations of OR and AND operators next to the number of keywords. Furthermore, this prevented us from generating search filters that only contained terms relating to a limited number of methods used to determine moderators or predictors. In short, we were directed to include both methodology and treatment related terms in the filters (improving generalisability and face validity).

Our selection of reference articles contained a large number of general medicine articles (126 of 198; 64%), most of which were RCTs. A total of 138 RCTs were in the set (42% of all RCTs in the six journals), while only seven papers described systematic reviews. This may explain the fact that terms related to trials yielded individually the highest Se and Sp. The results from the sensitivity analysis support this assumption, as the final set of best search filters performed much better on the core clinical journals (with a higher density of RCTs) compared to the rheumatology journals. This may imply that the search filters are more sensitive to RCTs than other types of studies. However, non-RCTs will still be picked up by our filters.

Our study has several limitations. The first relates to the selection methods we used, that is expanding only search terms and combinations, which yielded adequate Se and Sp. This selection method was used to prevent drops in performance measures while optimising other performance measures (e.g. dropping Sp while optimising Se and vice versa), while also bringing down the number of combinations to a more manageable size by only expanding search term combinations that reached performance thresholds. Although this approach is very similar to other work considered as best practice (Haynes et al., 1994), the selection method may become too strict in cases where search terms have a synergistic effect. In our view, the methods used make a

good compromise between restricting the amount of combinations and allowing good combinations to improve.

Second, we made no distinction between predictors and moderators when selecting articles while recognising a conceptual difference. However, this is unlikely to affect filter quality given that neither 'moderator' nor 'predictor' proved to be sensitive keywords.

Third, the search filters need to be tested in other medical domains. However, by excluding disease and field-specific keywords in the search filter generation we have tried to maximise generalisability. Many keywords in the search filters, such as 'randomi\*' or 'controll\*', seem to be related more to study design rather than moderator or predictor-specific analysis. Should specific designs be more prevalent in a specific field or time frame, and the performance of our filters may be reduced. Testing in other domains and/or time frames (or for instance, testing on the MCMASTER CLINICAL HEDGES database or Health Knowledge Refinery) may reveal these weaknesses and possibly prompt for amendments of these filter in future.

## Conclusions

The search filters developed within this study can help researchers to identify and retrieve papers on moderators or predictors of treatment effects. This represents an important step forward in identifying information to facilitate research on stratified or personalised health care.

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#### Competing interest

The authors declare they have no competing interests.

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#### Authors' contributions

All authors contributed to designing and setting up the research. MT, WK and CL performed the data collection. RvH, WK, MT and AB performed the analysis. AB and GJvdW contributed additionally to the interpretation of the results and helped interpreting the data. All authors reviewed the manuscript, provided feedback and read and agreed upon the final manuscript for submission.

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## Appendix A

### Search string

("Lancet"[Journal] OR "N Engl J Med"[Journal] OR "Arthritis Care Res (Hoboken)"[Journal] OR "Arthritis Rheum"[Journal] OR "Ann Rheum Dis"[Journal] OR "Arthritis Res Ther" [Journal]) AND 2011[pdat] NOT 2012[pdat].



## Appendix B

Articles identified as 'moderators relevant to rheumatology' (n = 198) during the manual search of the six journals for the year 2011 ('reference set' subset).

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## Appendix C - Predetermined search terms

Manually excluded terms		Fixed terms	
“Autoimmune diseases”[mesh]	two[tw]	vs	“Age Factors”[mesh]
“Middle aged”[mesh]	up	vs[tiab]	“Biological Markers”[mesh]
activ*	up[tiab]	vs[tw]	“Disease Progression”[mesh]
administr*	up[tw]	met*[mh]	“Effect Modifier,
adult*	base*		“Epidemiologi
adult*[tw]	base*[tiab]		Methods”[mesh]
after	base*[tw]		“Logistic
after[tiab]	baseline		Models”[mesh]
after[tw]	baseline[tiab]		“Predictive Value of
agent*	baseline[tw]		“Prognosis”[mesh]
agent*[tw]	care		“Risk
anti	ci		Factors”[mesh]
anti[tw]	ci[tiab]		“Treatment
antineoplastic	ci[tw]		Outcome”[mesh]
			adjust*
			analyse*
			associate*
			biomarker*



antirheumatic	confiden*	correlate*
arthritis[majr]	data	determinant*
arthritis[mh]	data[tiab]	effect*
Background	data[tw]	factor*
background[tiab]	epidemiology	identify*
background[tw]	epidemiology[sh]	improve*
Blood	includ*	interact*
blood[tw]	include*	logistic
chemotherapy[mh]	include*[tiab]	mediate*
chemotherapy[sh]	include*[tw]	model*
depart*	inhibit*	moderate*
End	inhibit*[tw]	multivariable
end[tiab]	inhibitor*	multivariate
end[tw]	inhibitor*[tw]	outcome*
find*	investigat*	predict*

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(continued) Table (continued)

Manually excluded terms		Fixed terms
find*[tiab]	mean*	predictive
find*[tw]	mean*[tiab]	predictor*
fund*	mean*[tw]	prognostic
fund*[tiab]	number*	regress*
fund*[tw]	number*[tiab]	relate*
Hospital	number*[tw]	relationship*
lii	patient*[ti]	response*
iii[tw]	plus	risk*
institute*	plus[tiab]	stratify*
interpret*	plus[tw]	subgroup*
Metastatic	point*	term
method*[mh]	point*[tiab]	therapy*
Middle	point*[tw]	treat*
middle[tw]	receiv*	univariate
objective*	receive*	
objective*[tiab]	receive*[tiab]	
objective*[tw]	receive*[tw]	

Over	registered
over[tw]	registered[tiab]
peptide*[mh]	registered[tw]
Per	respective*
per[tiab]	respective*[tiab]
per[tw]	respective*[tw]
protein*[majr]	total*
rheumatism	total*[tiab]
rheumatism[majr]	total*[tw]
rheumatism[mh]	versus
two	versus[tiab]
two[tiab]	versus[tw]

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## Appendix D - Classification of single search terms

Methods-terms		Treatment/outcome-terms	rat*
	“Double-blind method”[mesh]	“Outcome Assessment (Health care)”[mesh]	rate*
	placebo*		
AGE*[mh]	placebo*[tiab]	“Treatment Outcome”[mesh]	rate*[tiab]
age*[tiab]	placebo*[tw]	adverse*	rate*[tw]
aged[mesh]	random*	adverse*[tiab]	ratio*
analys*	random*[ti]	adverse*[tw]	ratio*[tiab]
analyse*	random*[tiab]	day*	ratio*[tw]
analyse*[tiab]	random*[tw]	day*[tiab]	reduc*
analyse*[tw]	randomi*	day*[tw]	reduce*
assess*	randomise*	death*	reduce*[tiab]
assess*[tiab]	randomise*[ti]	death*[tiab]	reduce*[tw]
assess*[tw]	randomise*[tiab]	death*[tw]	response*
assign*	randomise*[tw]	disease*[tiab]	response*[tiab]
assign*[tiab]	relat*	dosage	response*[tw]
assign*[tw]	trial*	dosage[tw]	risk*

(continued)

Table (continued)

Methods-terms		Treatment/outcome-terms	rat*
associ*	trial*[ti]	dose*	risk* [tiab]
associate*	trial*[tiab]	dose*[tiab]	risk*[tw]
associate*[tiab]	trial*[tw]	dose*[tw]	score*
associate*[tw]		effect*[tiab]	score*[tiab]
blind*		event*	score*[tw]
blind*[tw]		event*[tiab]	second*
center*	both methods and	event*[tw]	second*[tiab]
clinic*[tiab]	treatment or outcome terms	high*	second*[tw]
clinic*[tw]	differen*	high*[tiab]	secondary
clinicaltrial*	“Prognosis”[mesh]	high*[tw]	secondary[tiab]
clinicaltrial*[tiab]		higher	secondary[tw]
clinicaltrial*[tw]		higher[tiab]	sign*[tiab]
com*[tw]		higher[tw]	sign*[tw]
combin*		improve*	significan*
compar*		improve*[tiab]	significant*
compare*		improve*[tw]	significant*[tiab]
compare*[tiab]		incre*	significant*[tw]
compare*[tw]		incre*[tiab]	similar*

control*[tiab]	incre*[tw]	similar* [tiab]
controll*	increas*	similar*[tw]
controll*[tiab]	increase*	therap*
controll*[tw]	increase*[tiab]	therapeutic[mh]
double	increase*[tw]	therapeutic[tw]
double[tw]	interv*	therapy*[tiab]
estimat*	interv*[tiab]	tim*
factor*	interv*[tw]	time*
factor*[tiab]	lower*	time*[tw]
factor*[tw]	lower*[tiab]	times
follow*	lower*[tw]	treat*
follow*[tiab]	medic*	treat*
follow*[tw]	month*	treat*[ti]
group*	month*[tiab]	treat*[tiab]
group*[tiab]	month*[tw]	treat*[tw]
group*[tw]	more	treate*
hazard*	more[tiab]	treate*[tiab]
hazard*[tiab]	more[tw]	treate*[tw]
hazard*[tw]	mortality	week*

intent\*

mortality[tw]

week\*[tiab]

intent\*[tiab]

outcome\*

week\*[tw]

intent\*[tw]

outcome\*[tiab]

year\*

model\*[tw]

outcome\*[tw]

year\*[tiab]

multicenter

primar\*

year\*[tw]

multicenter[tw]

primary\*

phase

primary\*[tiab]

phase[tw]

primary\*[tw]