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Cost effectiveness of the determination of autoantibodies against cyclic citrullinated peptide in the early diagnosis of rheumatoid arthritis

A Konnopka,¹ K Conrad,² C Baerwald,³ H-H König¹

¹ Health Economics Research Unit, Department of Psychiatry, University of Leipzig, Leipzig, Germany; ² Institute of Immunology, Medical Faculty of the Technical University Dresden, Dresden, Germany; ³ Medical Clinic IV - Rheumatology, University Hospital, University of Leipzig, Leipzig, Germany

Correspondence to:
A Konnopka, University of Leipzig, Health Economics Research Unit, Department of Psychiatry, Johannisallee 20, D-04317 Leipzig, Germany; alexander.konnopka@medizin.uni-leipzig.de

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ABSTRACT

Objective: To estimate the incremental cost-effectiveness ratio (ICER) of antibodies against cyclic citrullinated peptides (aCCP) in the early diagnosis of rheumatoid arthritis (RA).

Methods: A Markov model was used to model 10-year progression of RA in patients first diagnosed with undifferentiated arthritis (UA) and to estimate the incremental costs and quality-adjusted life years (QALYs) of using aCCP additionally to American College of Rheumatology (ACR) criteria. The impact of later diagnosis and treatment due to non-use of aCCP was modelled as increased Health Assessment Questionnaire (HAQ) progression. Utilities were assigned to HAQ states for calculating QALYs. Uncertainty was analysed using univariate and probabilistic sensitivity analyses (Monte Carlo simulation).

Results: Baseline ICER was €930/QALY. Univariate sensitivity analyses identified the impact of later diagnosis on HAQ progression as a major source of uncertainty, resulting in an ICER range from "dominance" to €153 092/QALY, compared with a maximum ICER of €4870/QALY for other variables. Monte Carlo simulation resulted in a 95% uncertainty interval from -€3537/QALY (dominance) to €5429/QALY; when indirect costs were considered, Monte Carlo simulation resulted in a 95% uncertainty interval from -€78 115/QALY (dominance) to -€23 444/QALY (dominance).

Conclusions: Using aCCP in the diagnosis of RA in patients with UA is likely to be cost effective compared with using ACR criteria alone. When indirect costs are incorporated, aCCP seems to save costs. Clearly, more research is needed relating the effects of diagnosis and treatment on the long-term course and the resulting functional impairment of RA as measured by the HAQ.

Rheumatoid arthritis (RA) is a chronic inflammatory disease causing damage to joints and cartilages. Disease-modifying antirheumatic drugs (DMARDs) can slow down RA progress and reduce the extent of joint destruction,¹ particularly if they are used in earlier disease stages.²⁻³ Yet, diagnosing RA in earlier disease stages by American College of Rheumatology (ACR) criteria is often difficult,⁴ leading to a diagnosis of "undifferentiated arthritis" (UA) in patients not fulfilling the ACR criteria. In preclinical or early stages of RA with a symptom duration <2 years,⁵ for instance, rheumatoid factor is positive in only 20–45% of patients.⁶⁻⁸ Therefore, other laboratory measures can provide helpful additional information. Antibodies against cyclic citrullinated peptide (aCCP) present a highly specific marker of RA, occurring in 19–31% of

patients with rheumatoid factor-negative early RA.⁶⁻⁸ Through their additional use in the diagnosis of early RA, many patients with RA treated for UA (UA-RA) for up to several years can receive an adequate early treatment. This can slow down the long-term RA progression, improve health-related quality of life and avoid future costs. On the other hand, it increases the number of false positives, which may lead to unnecessary treatment and costs. These conflicting effects raise questions about the cost effectiveness of aCCP when consecutive treatment and relevant clinical end points are taken into account. As for therapeutic technologies, economic evaluation has also been postulated for diagnostic technologies.⁹

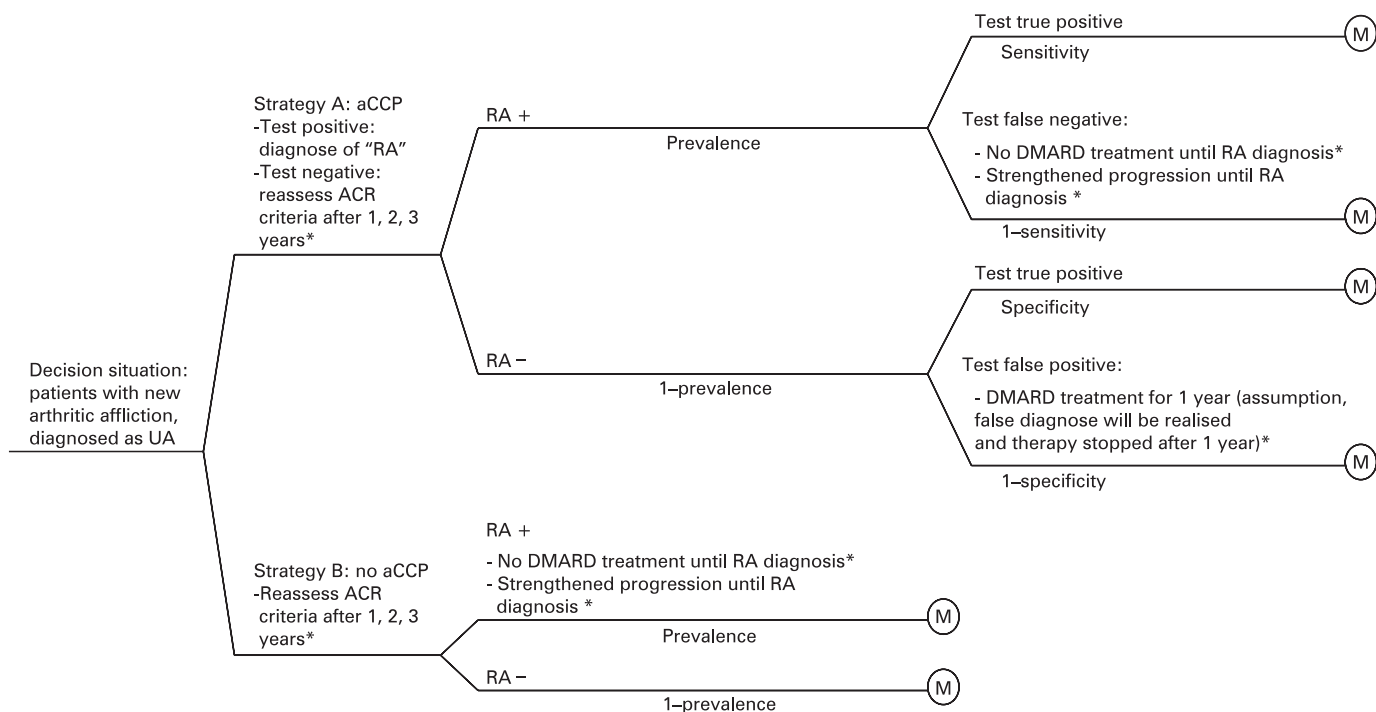
So-called Markov models may help us to examine the effect of additional aCCP use on RA progression, costs and health effects, by simulating the course of RA over time.¹⁰ They facilitate the comparison of long-term costs and effects of various diagnostic strategies with each other, enabling the determination of an incremental cost-effectiveness ratio (ICER). An ICER describes the ratio of the additional average costs of a strategy A compared with a strategy B to the additional average effects of strategy A compared with strategy B.¹¹ This study aims to determine the ICER of the additional use of aCCP (strategy A) in comparison with the use of ACR criteria alone (strategy B) for patients with a new diagnosis of UA.

METHODS

Study design

A cost-utility analysis was performed based on a decision analysis model. Costs were measured in euros, health effects in quality-adjusted life years (QALYs). QALYs are calculated by weighting the duration of health states with a preference-based score of health-related quality of life (utility), measured on a scale from 0 (death) to 1 (full health).

The decision analysis model was based on a hypothetical cohort of 40-year-old men and women (1:3 relationship) who saw a doctor the first time for arthritic pain. The doctor conducts normal diagnostic procedures, resulting in a diagnosis of UA. For this cohort two alternative diagnostic strategies were compared. With strategy A the aCCP status was determined and a positive test result brought an RA diagnosis, while with strategy B ACR criteria were assessed annually. The main outcome of the study was the ICER of strategy A compared with strategy B.



* - Time-dependent calculations are conducted within the Markov process

Figure 1 Structure of the model decision tree. aCCP, antibodies to cyclic citrullinated peptide; ACR, American College of Rheumatology; DMARD, disease-modifying antirheumatic drug; M, Markov model; RA, rheumatoid arthritis; UA, undifferentiated arthritis.

Decision analysis model

A decision analysis model was constructed, comprising a decision tree modelling the decision situation and Markov-processes modelling the progression of disease, costs and effects. Figure 1 represents the decision tree and table 1 reports the parameter values in the model. "Sensitivity" ("specificity") was the probability of a positive (negative) test result in people who will fulfil (not fulfil) ACR criteria for RA within 3 years after UA diagnosis.⁵

Markov models connect to ending points of the decision tree. For patients with RA a published Markov model¹² was used, containing six health states defined by the Health Assessment Questionnaire (HAQ)¹⁸ and the absorbing state "death" (for a schematic presentation see Kobelt *et al*¹²). The transition probabilities with which patients could alter from one health state to another were recorded from 183 Swedish patients with RA in the "Lund Study".¹² Owing to restrictions in cost data, the two worst health states were collapsed. According to the follow-up of the Lund study, the time horizon was set at 10 years. For patients without RA, the Markov model consisted of the health states "living" and "dead."

Mortality

We used normal age- and gender-specific mortality rate in the German population.¹⁹ In international publications statements about higher mortality among patients with RA vary^{20 21} and higher mortality is expected to occur only after longer disease duration as is the time horizon of the model.²⁰

Impact of late treatment

To model the differences in costs and health between strategies, it was necessary to quantify the yearly HAQ progress in

patients with UA-RA diagnosed with RA later compared with patients with UA-RA diagnosed earlier. Data on differences in HAQ progression were taken from international publications reporting HAQ progression either comparing "DMARD" with "placebo" or "early treatment" with "late treatment".² Based on these studies, it was assumed that the HAQ progression of patients with undiagnosed RA exceeds the HAQ progression of patients with diagnosed RA by 0.1 HAQ a year.

To integrate this impact in the Markov models, five additional health states (same HAQ classes) were generated for undiagnosed patients. For these health states, transition probabilities were modified to simulate the difference in progression as an increased probability of moving to worse health states until diagnosis, after which the original transition probabilities were used. Since normal transition probabilities already represented patients receiving treatment, this was difficult because it required the addition of further HAQ progression to the HAQ progression of patients receiving treatment. This resulted in an overestimation of the absolute HAQ progression of undiagnosed patients. Despite this problematic assumption, we considered this way as acceptable, because our main focus was not on the absolute HAQ progression but on the difference in HAQ progression between the two strategies.

For patients with UA-RA in strategy B or with a false negative test result in strategy A the probabilities of being diagnosed as patients with RA 1 or 2 years after onset of symptoms (table 1) were calculated from the study of van Gaalen *et al*.⁵ For patients with UA-RA not yet diagnosed as patients with RA after 2 years, it was assumed that RA diagnosis was definitively established after 3 years. Table 2 shows the distribution of patients over health states for patients with RA diagnosed by aCCP and after 1, 2 or 3 years, respectively.

Table 1 Parameter values used in the decision analysis model with the range used for univariate sensitivity analyses and the distribution used for Monte Carlo simulation

Parameter	Source	Base value	Range used in univariate sensitivity analyses	Distribution used in Monte Carlo simulation
General and test parameters				
Prevalence of RA in UA	5	0.400	0.346–0.453	β (127; 191)*
Specificity of aCCP	5	0.974	0.947–0.988	β (186; 5)*
Sensitivity of aCCP	5	0.504	0.417–0.591	β (64; 63)*
Proportion of men		0.25	(None)	(None)
Proportion of women		0.75	(None)	(None)
Probability of getting diagnosed after:				
1 Year, aCCP test false negative	5	0.730	0.621–0.840	β (46; 17)*
2 Years, aCCP test false negative	5	0.824	0.636–0.932	β (14; 3)*
1 Year, no aCCP test done	5	0.811	0.743–0.879	β (103; 24)*
2 Years, no aCCP test done	5	0.792	0.626–0.902	β (19; 5)*
Impact of late diagnosis on HAQ progression	12	0.1	0.01–0.15	(None)
Age	(None)	40	30–60	(None)
Model run time (years)	12	10	5–10	(None)
Starting distribution of Markov model				
State 1	12	0.27	1\$	(None)
State 2	12	0.33	0\$	(None)
State 3	12	0.26	0\$	(None)
State 4	12	0.10	0\$	(None)
State 5	12	0.04	0\$	(None)
Yearly direct costs, except costs of aCCP test				
Diagnosed male state 1	13 14	1764	1461–2067	Base value + s \times N (0; 1)†
Diagnosed male state 2	13 14	3449	2670–4227	Base value + s \times N (0; 1)†
Diagnosed male state 3	13 14	4102	3258–4946	Base value + s \times N (0; 1)†
Diagnosed male state 4	13 14	5753	4357–7148	Base value + s \times N (0; 1)†
Diagnosed male state 5	13 14	9677	5860–13 495	Base value + s \times N (0; 1)†
Undiagnosed male state 1	13 14	1210	978–1442	Base value + s \times N (0; 1)†
Undiagnosed male state 2	13 14	2513	1860–3166	Base value + s \times N (0; 1)†
Undiagnosed male state 3	13 14	2811	2137–3485	Base value + s \times N (0; 1)†
Undiagnosed male state 4	13 14	4536	3306–5767	Base value + s \times N (0; 1)†
Undiagnosed male state 5	13 14	8519	4865–12 173	Base value + s \times N (0; 1)†
Diagnosed female state 1	13 14	2093	1734–2452	Base value + s \times N (0; 1)†
Diagnosed female state 2	13 14	3970	3074–4866	Base value + s \times N (0; 1)†
Diagnosed female state 3	13 14	4668	3708–5628	Base value + s \times N (0; 1)†
Diagnosed female state 4	13 14	6771	5128–8414	Base value + s \times N (0; 1)†
Diagnosed female state 5	13 14	11 005	6663–15 346	Base value + s \times N (0; 1)†
Undiagnosed female state 1	13 14	1501	1213–1788	Base value + s \times N (0; 1)†
Undiagnosed female state 2	13 14	2970	2198–3742	Base value + s \times N (0; 1)†
Undiagnosed female state 3	13 14	3288	2500–4076	Base value + s \times N (0; 1)†
Undiagnosed female state 4	13 14	5471	3987–6956	Base value + s \times N (0; 1)†
Undiagnosed female state 5	13 14	9767	5577–13 956	Base value + s \times N (0; 1)†
Costs of aCCP test	15	30	15–45	(None)
Indirect costs multiplier				
Work capacity state 1	16	0.5000	0.250–0.750	Base value \times N (1; 0.255)‡
Work capacity state 2	16	0.3770	0.189–0.566	Base value \times N (1; 0.255)‡
Work capacity state 3	16	0.2345	0.117–0.352	Base value \times N (1; 0.255)‡
Work capacity state 4	16	0.0547	0.027–0.082	Base value \times N (1; 0.255)‡
Work capacity state 5	16	0.0317	0.016–0.048	Base value \times N (1; 0.255)‡
Utilities				
Utility state 1	17	0.768	0.750–0.786	β (1568.65; 473.86)*
Utility state 2	17	0.645	0.608–0.682	β (412.88; 227.25)*
Utility state 3	17	0.539	0.494–0.584	β (258.5; 221.09)*
Utility state 4	17	0.488	0.426–0.551	β (119.52; 125.4)*
Utility state 5	17	0.239	0.176–0.302	β (41.85; 133.26)*
Discount rate	(None)	0.05	0–0.1	(None)

*A β Distribution (α ; β); †a normal distribution (mean; standard deviation) multiplied by the standard error (s) of cost data; ‡a normal distribution (mean; standard deviation); \$An alternative starting distribution, but no interval.

aCCP, antibodies to cyclic citrullinated peptide; HAQ, Health Assessment Questionnaire; N, normal distribution; RA, rheumatoid arthritis; UA, undifferentiated arthritis.

Table 2 Percentage distribution of Markov cohort over health states for RA diagnosis immediately and after 1, 2 or 3 years; state "death" omitted

RA diagnosis at	Markov cycle (in years)										
	0	1	2	3	4	5	6	7	8	9	10
Health state 1 (HAQ<0.5)											
Year 0	27	24	22	21	20	19	19	18	18	17	17
Year 1	27	19	19	18	18	18	17	17	17	17	17
Year 2	27	19	15	16	16	16	16	16	16	16	16
Year 3	27	19	15	12	13	14	14	15	15	15	15
Health state 2 (0.5<HAQ<1.1)											
Year 0	33	33	32	32	31	31	31	30	30	30	30
Year 1	33	32	31	30	30	30	30	30	29	29	29
Year 2	33	32	30	28	28	28	28	29	29	29	29
Year 3	33	32	30	27	26	27	27	27	28	28	28
Health state 3 (1.1<HAQ<1.5)											
Year 0	26	26	27	28	28	28	29	29	29	29	29
Year 1	26	25	27	28	29	29	29	29	30	30	30
Year 2	26	25	26	28	29	30	30	30	30	30	30
Year 3	26	25	26	26	29	30	30	30	30	30	30
Health state 4 (1.5<HAQ<2.1)											
Year 0	10	13	14	15	16	16	17	17	17	18	18
Year 1	10	17	17	17	17	18	18	18	18	18	18
Year 2	10	17	21	20	20	19	19	19	19	19	19
Year 3	10	17	21	24	22	22	21	20	20	20	19
Health state 5 (HAQ>2.1)											
Year 0	4	4	4	5	5	5	5	5	6	6	6
Year 1	4	6	6	6	6	6	6	6	6	6	6
Year 2	4	6	9	8	7	7	7	6	6	6	6
Year 3	4	6	9	11	9	8	8	7	7	7	7

HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis.

Costs

Cost data were taken from published reports. The following direct costs were considered: aCCP test,¹⁵ inpatient and outpatient treatment,¹³ rehabilitation,¹⁵ DMARD and non-DMARD drugs (including monitoring and side effects)¹³ and "out of pocket" expenses.¹⁴ All data were from Germany, except aCCP costs, which were Swiss data (conversion: 1.5 SFr = €1). Costs of inpatient and outpatient treatment and rehabilitation were reported according to the HAQ intervals of the health states used. Out of pocket expenses were reported and used for HAQ values ≤ 1.5 and > 1.5 . Average drug costs were calculated by weighting costs of various agents with their prescription frequency in Germany.²² Subsequently, a study by Kobelt *et al*¹² was used to derive HAQ-dependent multipliers for drug costs. Furthermore, a study of Huscher *et al*²³ was used to derive multipliers for gender differences for all direct costs. It was assumed, that patients not yet diagnosed with RA cause all costs described, except DMARD costs, whereas diagnosed patients with RA cause all costs (table 1). For false positive non-RA patients, it was assumed that they received DMARDs for 1 year (model cycle length), after which the diagnostic mistake was then recognised and DMARD treatment stopped.

Separately, we conducted an analysis considering indirect costs based on diminished productivity. Productivity was the sum of age- and gender-specific German gross salaries²⁴ and employers' contributions to social security.²⁵ Productivity in

patients with UA-RA and patients with RA was multiplied by an HAQ-dependent factor reflecting disease-related loss of productivity.¹⁶

Future costs were discounted at 5% according to German guidelines for economic evaluation.²⁶

Utilities

QALYs were calculated by weighting the duration of health states with published HAQ-dependent Euroqol-5 dimensions (EQ-5D) index values¹⁷ as utility scores. Future QALYs were discounted at 5% analogously to costs.

Sensitivity analysis

Since there was uncertainty about the true values of the model parameters, the robustness of the model was tested in univariate sensitivity analysis by creating meaningful intervals around the base values, within which the parameters could vary (table 2). For parameters lending themselves to a meaningful distribution (table 2), a Monte Carlo simulation was conducted.²⁷ For this purpose, instead of numerical values, distributions were assigned to parameters, from which values were randomly sampled for each simulation. Conducting 10 000 simulations generated a probability distribution of the ICER.

For the base model the initial distribution of patients among the health states of the Markov model was taken from the Lund

Table 3 Results of univariate sensitivity analyses

Parameter changed*	ICER (€/QALY)	
	Lower range	Upper range
Prevalence of RA	523	1472
Specificity of aCCP	398	1954
Sensitivity of aCCP	485	1592
Probability of getting diagnosed after:		
1 Year, aCCP test false negative	762	1133
2 Years, aCCP test false negative	909	967
1 Year, no aCCP test done	723	1198
2 Years, no aCCP test done	887	960
Impact of late diagnosis on HAQ progression	Dominance	153 092
Age	783	1914
Model run time	270	4870
Direct costs, except costs of aCCP test	720	1139
Costs of aCCP test	14	1845
Utilities	832	1052
Discount rate	Dominance	3628

*Parameters changed as described in table 1 (column 4).

aCCP, antibodies to cyclic citrullinated peptide; HAQ, Health Assessment Questionnaire; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RA, rheumatoid arthritis.

study.¹² Since our hypothetical cohort is in early RA stages, we conducted an analysis with all subjects starting in the best health state. All calculations were accomplished with the software DATA Pro (TreeAge Software, Williamstown, Massachusetts, USA) and Excel 2000 (Microsoft, USA).

RESULTS

Base results

With base values, the mean costs for strategy A (aCCP) were €15 010 per patient with UA, compared with €14 995 with strategy B (no aCCP), corresponding to incremental costs of €15.23 per patient for strategy A. Mean effects were 7.1237 QALYs per patient with UA for strategy A compared with 7.1073 QALYs for strategy B, corresponding to incremental effects of 0.0164 QALYs. An ICER of €930/QALY resulted from these increments. When indirect costs were considered, strategy A was dominant over strategy B.

Univariate sensitivity analysis

Table 3 shows the results of the univariate sensitivity analysis. The lower ICER limit ranged between “dominance” and €909/QALY. The upper ICER limit ranged between €960 and

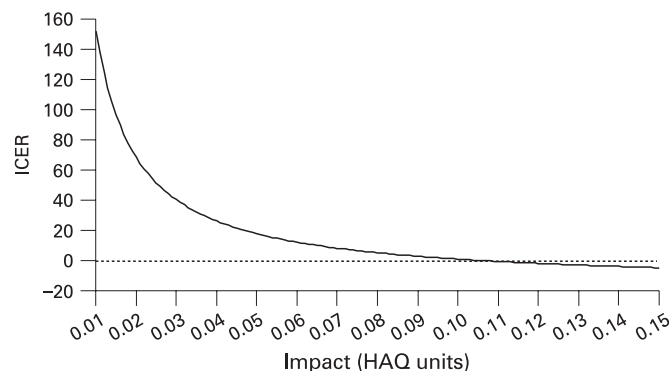


Figure 2 Incremental cost-effectiveness ratio (ICER) in thousands of euros depending on the impact of late diagnosis and treatment on Health Assessment Questionnaire (HAQ) progression.

€153 092/QALY. Interestingly, the upper ICER limit was only €4870/QALY except for the variation of the impact of late diagnosis and treatment on HAQ progression. Thus, this impact was the only measure whose variation caused considerable changes in the ICER. This result also appeared in a weaker form when indirect costs were considered or when the initial distribution “all patients in state 1” was used: for indirect costs, variations of the impact of late diagnosis and treatment on HAQ progression resulted in an ICER between “dominance” and €102 038/QALY, whereas strategy A was dominant for variations of all other parameters. If all patients were in state 1, the ICER for variations of the impact of late diagnosis and treatment on HAQ progression was between “dominance” and €91 067/QALY, whereas for variations of all other parameter values strategy A was dominant.

Figure 2 shows the ICER depending on the impact of late diagnosis and treatment on HAQ progression. While the ICER was €153 092/QALY with an impact of 0.01 HAQ points, it was already less than €50 000/QALY with an impact of 0.026, and with an impact of 0.05 (50% base value) it was €17 849/QALY. With an impact of 0.106 or more, strategy A was dominant.

Monte Carlo simulation

Figure 3 shows the incremental costs and effects from 10 000 simulations on the cost-effectiveness plane. The 95% uncertainty interval of incremental costs was between –€62.27 and €85.74 (median €15.92). The 95% uncertainty interval of the incremental effects was between 0.0114 and 0.0222 QALYs (median 0.0162 QALYs). Median ICER was €996/QALY and the 95% uncertainty interval was between –€3537/QALY (dominance) and €5429/QALY.

Owing to the large uncertainty associated with the impact of later diagnosis and treatment on HAQ progression Monte Carlo simulations were conducted for several values of this impact. If the impact was 0.02; 0.03; 0.04; 0.05; 0.06; 0.075 or 0.1, ICER was beneath €80 645; €47 523; €31 548; €21 905; €16 020; €10 208; or €4727/QALY, respectively, in 95% of simulations.

When Monte Carlo simulation was conducted with indirect costs, the 95% uncertainty interval of incremental costs was between –€1344 and –€360 (median –€803) and the 95% uncertainty interval of incremental effects was between 0.0113 and 0.0220 QALYs (median 0.0162 QALYs). Median ICER was –€50 120/QALY (dominance), and the 95% uncertainty interval was between –€78 115/QALY (dominance) and –€23 444/QALY (dominance).

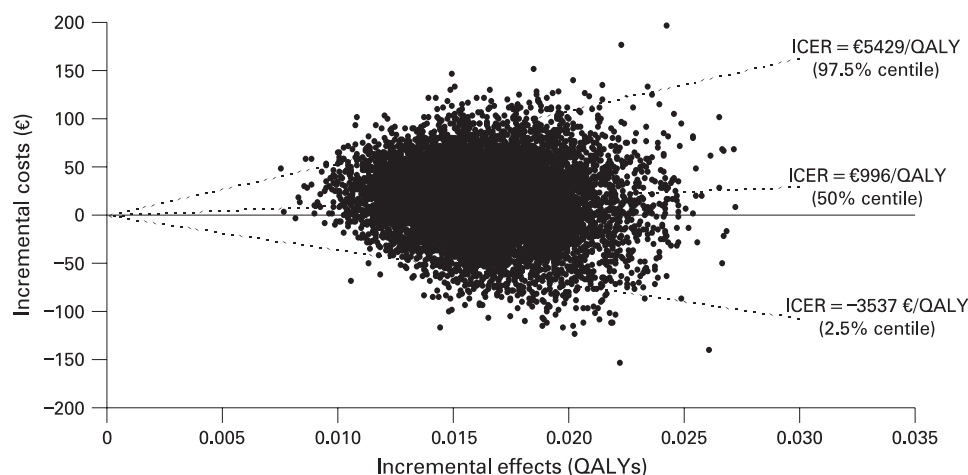
DISCUSSION

To our knowledge, this study is the first examining the cost effectiveness of aCCP in early diagnosis of RA. The results show that determination of aCCP with an ICER of €930/QALY presents a comparatively cost-effective diagnostic strategy in early diagnosis of RA in patients with UA. Univariate sensitivity analysis indicates that the findings are relatively stable for all varied parameters except the impact of late diagnosis on HAQ progression. When this impact was neglected, ICER varied between dominance and €4870/QALY. However, variations of this impact led to substantial changes of the ICER between dominance and €153 092/QALY.

One must caution that this impact was subject to a substantial variation of –90% to +50%. If the impact had been varied as other parameters with comparable uncertainty between –/+50% ICER would have ranged from dominance to

Extended report

Figure 3 Distribution of incremental costs and effects in the cost-effectiveness plane. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.



€17 849/QALY. But a larger variation at the bottom seemed necessary for several reasons. First, this impact was derived from studies whose results were only partially applicable to our model. Scott *et al*¹ and Strand *et al*²⁸ reported comparisons of DMARD versus placebo. This was comparable to the model's situation, since patients with RA received DMARD treatment, while we assumed only symptomatic treatment for patients with UA-RA. However, symptomatic treatment can positively influence HAQ progression as well. Furthermore, Scott *et al* and Strand *et al* refer to patients with RA. These patients are in more advanced disease stages than patients with UA, making an estimation of the impact based on these studies possibly strongly exaggerated. The findings of Nell *et al*² seem to be better suited. Nell *et al* examined the effect of the starting point of treatment on HAQ progression in early RA. However, compared with our model this moment is still relatively late. Furthermore, the study of Nell *et al* had small sample sizes and the difference between early and late diagnosis was 9 months, compared with 12 in our model. Second, the method of including the impact in our model led to a substantial overestimation of absolute HAQ progression of undiagnosed patients, and thus demanded a wide variation at the bottom range within sensitivity analysis.

A further factor largely influencing the ICER was the indirect costs. Owing to data availability, German productivity data were adjusted by using HAQ-dependent multipliers from a Swedish sample. These multipliers should largely depend on disease activity whose relative influence on direct as well as indirect costs should at least be similar over countries. Also, the price of the aCCP test was converted from Swiss administrative data, which should be similar to Germany. Nevertheless, transferability of these cost data to Germany is limited and thus a source of uncertainty.

Further points in our study must be critically viewed. It is not certain if the Markov model and, in particular, the transition probabilities—both derived from patients with manifest RA—can be applied to patients with UA-RA. The cycle length for the Markov model was set at 1 year. This was necessary, since almost all time-dependent variables were only present in the form of annual values. This meant that we had to work with the assumption that the ACR criteria in patients with UA-RA with false negative test results, or in strategy B (no aCCP test) were only gathered once a year. Based on clinical reality, this time period is quite long. Owing to lack of suitable data for patients with UA-RA, we used data from the Swedish sample

(from where the transition probabilities were derived) for the initial distribution in the Markov model.¹² Since these patients were patients with RA, the initial probability of severe health states may be too high. The analysis under the assumption that all patients start in the best health state, led to a more favourable result (dominance of strategy A (aCCP test)) over strategy B (no aCCP test)) compared with base analysis, as shown in sensitivity analysis. The time horizon of the model was limited to 10 years. Since no additional costs from the use of aCCP can be expected after 10 years, while the delayed progression of disease with early treatment may still lead to an additional effect (QALYs), ICER is unfavourably influenced by the limited time horizon of the model. This time effect is probably even stronger when considering indirect costs. Patients with delayed treatment can have additional indirect costs compared with patients treated early, based on the advanced disease progression. This is, because indirect costs increase with increasing impairment of functioning due to progressing bone erosion, and because an increased length of disease may increase mortality owing to systemic manifestations of RA. In the light of the chronic character of RA, these factors must be considered in interpreting the results of this study.

Finally, one must note that the model presented here is based on classification criteria which might not be applied in daily clinical practice where other criteria might have better diagnostic and predictive properties,²⁹ reducing the validity of our model. Despite the fact that this elusive bias occurs in both strategies and the ICER is based on differences between strategies, the possibility of an influence on the ICER cannot be excluded.

CONCLUSIONS

Taken together, aCCP is likely to be a very cost-effective or even cost-saving diagnostic complement in early diagnosis of RA for patients with UA. This is especially true when considering indirect costs. A more certain decision on whether aCCP is cost effective will depend on more insight into the clinical data that need to be collected, in particular on the impact of a late diagnosis and introduction of treatment on the long-term progression of disease and the HAQ, which was the largest source for uncertainty of the ICER. This also means that cost effectiveness may (favourably) change, depending on changes in therapeutically possibilities. Improvement of the long-term prognosis of RA with early interventions, will improve the ICER of early diagnostic tests like aCCP.

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