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Cost effectiveness analysis of *HLA-B*58:01* genotyping prior to initiation of allopurinol for gout

Catrin O. Plumpton[1], Ana Alfirevic[2], Munir Pirmohamed[2] and Dyfrig A. Hughes[1,2]

Abstract

Objective. To determine whether prospective testing for *HLA-B*58:01*, as a strategy to prevent serious adverse reactions to allopurinol in patients with gout, is cost-effective from the perspective of the National Health Service in the UK.

Methods. A systematic review and meta-analysis for the association of *HLA-B*58:01* with cutaneous and hypersensitivity adverse drug reactions informed a decision analytic and Markov model to estimate lifetime costs and outcomes associated with testing *vs* standard care (with febuxostat prescribed for patients who test positive). Scenario analyses assessed alternative treatment assumptions and patient populations.

Results. The number of patients needed to test to prevent one case of adverse drug reaction was 11 286 (95% central range (CR): 2573, 53 594). Cost and quality-adjusted life-year (QALY) gains were small, £103 (95% CR: £98, £106) and 0.0023 (95% CR: −0.0006, 0.0055), respectively, resulting in an incremental cost-effectiveness ratio (ICER) of £44 954 per QALY gained. The probability of testing being cost-effective at a threshold of £30 000 per QALY was 0.25. Reduced costs of testing or febuxostat resulted in an ICER below £30 000 per QALY gained. The ICER for patients with chronic renal insufficiency was £38 478 per QALY gained.

Conclusion. Routine testing for *HLA-B*58:01* in order to reduce the incidence of adverse drug reactions in patients being prescribed allopurinol for gout is unlikely to be cost-effective in the UK; however testing is expected to become cost-effective with reductions in the cost of genotyping, and with the future availability of cheaper, generic febuxostat.

Key words: allopurinol, pharmacogenetics, cutaneous adverse drug reaction, cost-effectiveness analysis, HLA-B*58:01

CLINICAL SCIENCE

Rheumatology key messages

- *HLA-B*58:01* is associated with severe adverse drug reactions to allopurinol in patients with gout.
- Routine testing of gout patients for *HLA-B*58:01* is currently not cost-effective in the UK.
- *HLA-B*58:01* genotyping of gout patents is cost-effectiveness if the price of testing and febuxostat reduces.

Introduction

Gout is a common inflammatory condition characterized by acute attacks (flares), which are episodes of severe joint pain usually with redness, swelling and tenderness of the joint, and it is associated with increased risk of cardiovascular disease [1, 2]. Gout affects ~2.5% of the population and is most prevalent in older men [3].

Standard treatment for the long term management of gout includes urate lowering agents, with allopurinol accounting for 89% of prescriptions in the UK between 2000 and 2005 [4]. Allopurinol is generally well tolerated, but is associated with rare but severe cutaneous adverse drug reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), affecting approximately 7 in 10 000 patients [5]. SCARs are associated with high mortality—up to 30% in the case of TEN [6]. Allopurinol is also associated with hypersensitivity

[1]Centre for Health Economics and Medicines Evaluation, Bangor University, Wales and [2]Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK

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Correspondence to: Dyfrig Hughes, Centre for Health Economics and Medicines Evaluation, Bangor University, Ardudwy, Normal Site, Holyhead Road, Bangor, Wales, LL57 2PZ, UK.
E-mail: d.a.hughes@bangor.ac.uk

adverse drug reactions (ADRs) [hereafter referred to as drug reaction with eosinophilia and systematic symptoms (DRESS)], including drug-induced hypersensitivity syndrome, also sometimes called allopurinol hypersensitivity syndrome or hypersensitivity syndrome [7].

Genetic association studies have identified the presence of the *HLA-B*58:01* allele to be an important risk factor for allopurinol-induced SJS or TEN, with an odds ratio of 96.6 (95% CI: 24.5, 381.0) [8]. *HLA-B*58:01* is present in 15–18% of certain Asian populations but is less common (1–2%) in European populations [9]. Other risk factors for allopurinol hypersensitivity include high dose, renal impairment and concomitant use of diuretics [10].

While routine testing is not currently recommended by the Food and Drug Administration or the European Medicines Agency [11], the ACR guidelines note that genotyping should be considered in selected patients at elevated risk of ADRs, including those with chronic renal insufficiency [12]. There are no randomized controlled trials of routine testing; however prospective cohort studies have suggested effectiveness in Taiwanese populations [13] and Korean patients with chronic renal insufficiency [14]. In both studies, patients who tested positive for *HLA-B*58:01* either avoided allopurinol or were administered allopurinol on a 28-day induction programme. No cases of SCAR occurred in either study, compared with expected rates of 0.3% [13] and 18% [14].

Many healthcare systems require evidence of efficiency for broader adoption of health technologies, including pharmacogenetics tests. Existing economic analyses have indicated that genotyping for *HLA-B*58:01* may be cost-effective in both Thailand and Korea [15, 16], but not in Singapore [17]. The aim of the present analysis is to estimate the cost-effectiveness of *HLA-B*58:01* genotyping prior to prescription of allopurinol in the UK healthcare setting.

Methods

Overview

A cohort model was used to track patients with chronic gout over a lifetime. Patients either receive allopurinol or are first genotyped for *HLA-B*58:01* before being prescribed either allopurinol or febuxostat, conditional on test result. Febuxostat is recommended by the National Institute for Health and Care Excellence in the UK as a second line treatment if allopurinol is not tolerated or is contraindicated. The analysis adopts the costing perspective of the National Health Service (NHS) in the UK assuming cost year 2014. Health outcomes were measured as quality-adjusted life-years (QALYs). Costs and QALYs were discounted after 1 year at a rate of 3.5% per annum. The base-case population was chosen to be representative of the gout population in the UK, 81% male, with a mean age at diagnosis of 61.6 years [4].

The model, which is depicted in Fig. 1, was adapted from the decision analysis of Beard *et al*. [18], incorporating 3-month decision trees to capture the time during which the majority of serious ADRs are likely to occur [5, 19]. A Markov model, with a cycle length of 3 months and with half-cycle correction, captured the lifetime sequelae of SJS, TEN and DRESS, and the long term differences in costs and effectiveness of alternative urate lowering agents. States within the model were defined according to the following: (i) serum uric acid (sUA) concentration <360 μmol/l; 360 μmol/l $<$ sUA <475 μmol/l; 475 μmol/l $<$ sUA <595 μmol/l; and sUA >595 μmol/l; they reflect whether patients had experienced SJS, TEN or DRESS, with an option for acute flares, and death (Fig. 1). We assumed sUA to remain constant for individual patients, based on data from the EXCEL study, which indicated that 75–100% of patients who achieved sUA <360 μmol/l maintained this over the remainder of the study [20].

Treatment pathway

For standard care, all patients are prescribed allopurinol, titrated to 300 mg/day during the first 3 months. Patients who are genotyped for *HLA-B*58:01* or who experience a serious ADR with allopurinol switch to febuxostat 80 mg/day, given there is no evidence of cross-reactivity [21, 22]. Patients experiencing a serious ADR with febuxostat (which is far less likely) [23], discontinue urate lowering therapy altogether.

The clinical effectiveness for allopurinol, febuxostat and symptomatic flare management was considered in terms of the end point of reducing sUA to <360 μmol/l, consistent with existing clinical guidelines for the management of gout [12, 24, 25], and in terms of prevention (or in the prophylaxis period, provocation) of gout flares. Prophylactic treatment with colchicine (500 μg twice daily) was modelled for 3 months following initiation of allopurinol, or for 6 months following initiation of febuxostat [26]. The use of NSAIDs is assumed for all patients, but not probenecid, which is not listed in the British National Formulary.

Model parameters

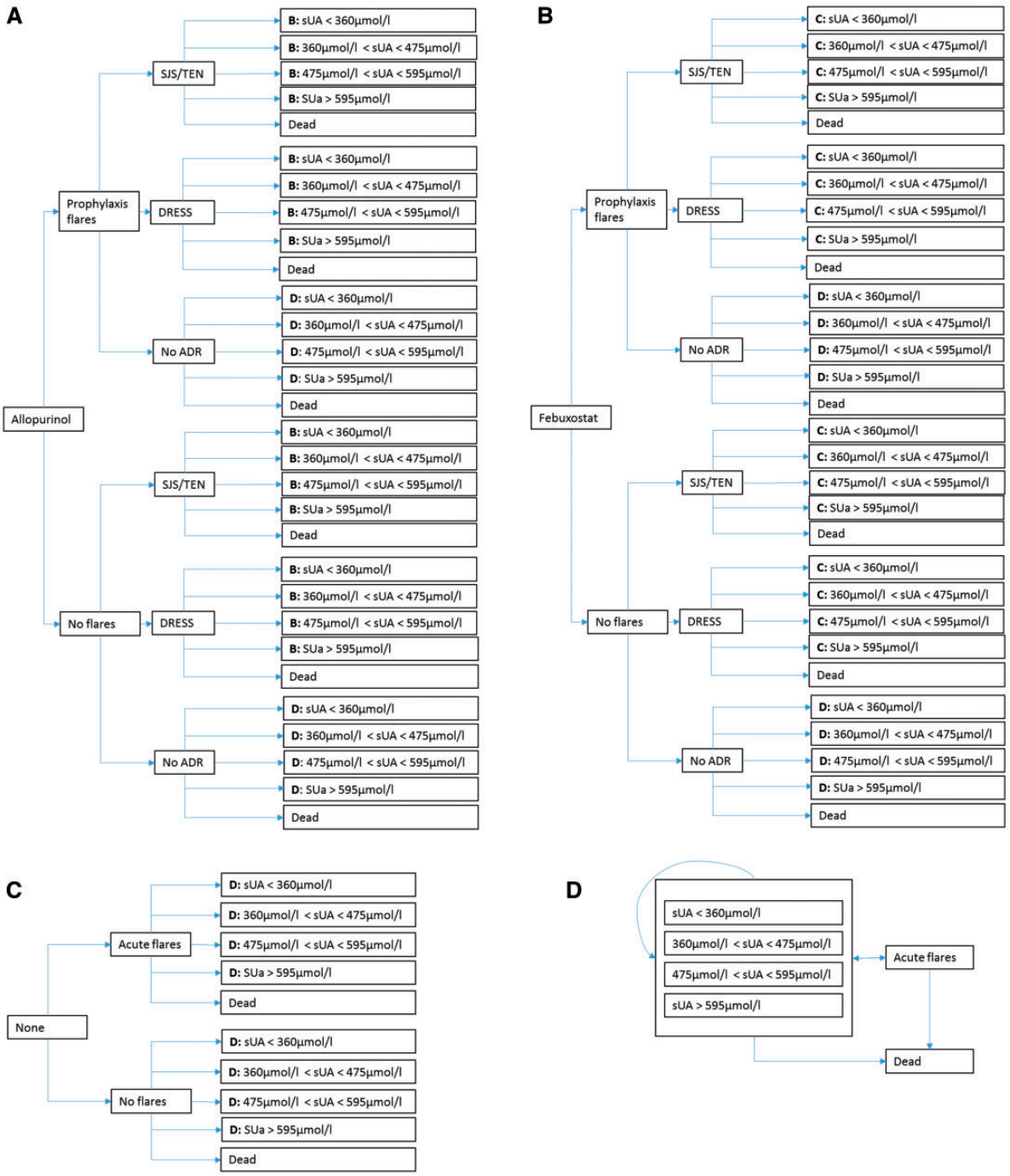
Parameter estimates were obtained from purposive reviews of the literature and are listed in Table 1.

Clinical effectiveness

The risk ratios for sUA <360 μmol/l with febuxostat 80 mg/day and allopurinol 300 mg/day were taken from the Cochrane review and meta-analysis based on data from the FACT [30], APEX [30] and CONFIRMS [31] trials. The risk-ratio for achieving sUA to <360 μmol/l with no treatment was taken from the Cochrane review and meta-analysis of studies comparing allopurinol 300 mg/day and placebo [27].

For patients who did not achieve sUA <360 μmol/l, the distribution of patients across the non-response sUA categories was allocated according to those indicated in Beard *et al*. [18], taken from the FACT and APEX studies [29, 30]. The distribution of patients across sUA categories for no treatment was assumed to be the same as for allopurinol.

Fig. 1 Schematic representation of the decision analytic model



Patients in the no test scenario all enter the model at A, while patients in the test scenario enter the model at either A or B dependent upon test result. Patient flow between each 3-month model is represented at the leaf nodes. Where patients reach the Markov model (model D) before the end of 12 months, the first cycles (up until 12 months) are treated as the run-in period. DRESS: drug reaction with eosinophilia and symptomatic symptoms; SJS: Stevens-Johnson syndrome; sUA: serum uric acid concentration; TEN: toxic epidermal necrolysis.

Table 1 Model inputs: transition probabilities, costs and utilities

Parameter	Mean	Distribution for probabilistic sensitivity analysis	Univariate sensitivity analysis		Reference
			Lower range	Upper range	
Transition probabilities					
Prevalence of *HLA-B*58:01* (European mean)	0.0113	β (27 340, 202 446)	0.0108	0.0119	[9]
P(SJS/TEN|allopurinol) within 3 months of initiation	0.0002	Normal (0.0002, 0.00007)	0.00002	0.0003	[15, 19]
P(DRESS|allopurinol) within 3 months	0.0011	β (2, 1835)	0.0001	0.0030	[26]
P(SJS/TEN|febuxostat) within 3 months of initiation	0.00010	β (1, 9999)	0.00000	0.00037	[23]
P(DRESS|febuxostat) within 3 months of initiation	0.00010	β (1, 9999)	0.00000	0.00037	[23]
Sensitivity of test (SJS/TEN)	0.9285	β (144.64, 8.07)	0.8984	0.9732	Meta-analysis
Specificity of test (SJS/TEN)	0.8907	β (311.64, 42.01)	0.8432	0.9110	Meta-analysis
Sensitivity of test (DRESS)	0.9348	β (56.34, 3.93)	0.8387	0.9753	Meta-analysis
Specificity of test (DRESS)	0.8470	β (20.51, 3.63)	0.6544	0.9441	Meta-analysis
P(360μmol/l|allopurinol)	0.3800	β (497.8, 812.2)	0.3539	0.4064	[27]
Proportion of non-responders with (360 μmol/l <sUA <475 μmol/l|allopurinol)	0.7900	β (641.638, 170.562)	0.7613	0.8173	[18]
Proportion of non-responders with (475μmol/l <sUA <595 μmol/l|allopurinol)	0.1750	β (142.135, 670.065)	0.1497	0.2019	[18]
Proportion of non-responders with (sUA >595 μmol/l|allopurinol)	0.0350	β (28.247, 783.773)	0.0235	0.0487	[18]
Risk ratio UA febuxostat *vs* allopurinol	1.8182	γ (208.2823, 0.0088)	1.5873	2.0833	[28]
P(360 μmol/l|febuxostat)	0.6909				RR*allopurinol
Proportion of non-responders with (360 μmol/l <sUA <475 μmol/l|febuxostat)	0.7410	β (299.5796, 104.7113)	0.6973	0.7825	[18]
Proportion of non-responders with (475μmol/l <sUA <595 μmol/l|febuxostat)	0.2130	β (86.114, 318.177)	0.1745	0.2542	[18]
Proportion of non-responders with (sUA >595 μmol/l|febuxostat)	0.0460	β (18.597, 385.694)	0.0278	0.0684	[18]
Risk risk sUA none *vs* allopurinol	0.0203	γ (0.0898, 0.1586)	0.0029	0.1439	[27]
Proportion of non-responders with (360 μmol/l <sUA <475 μmol/l|no treatment)	0.7900	β (641.638, 170.562)	0.7613	0.8173	As for allopurinol
Proportion of non-responders with (475 μmol/l <sUA <595 μmol/l|no treatment)	0.1750	β (142.135, 670.065)	0.1497	0.2019	As for allopurinol
Proportion of non-responders with (sUA >595 μmol/l|no treatment)	0.0350	β (28.247, 783.773)	0.0235	0.0487	As for allopurinol
P(initial flares|allopurinol)	0.1402	β (166, 1184)	0.1210	0.1605	[29, 30, 31]
Risk ratio of initial flare, febuxostat *vs* allopurinol	1.3130	γ (43.2461, 0.0311)	0.9730	1.7720	[28]
P(acute flares|sUA <360 μmol/l)	0.0874	β (311.5008, 3252.5819)	0.0784	0.0969	[18]
P(acute flares|360 μmol/l <sUA <475 μmol/l)	0.0989	β (307.8354, 2804.7567)	0.0887	0.1096	[18]
P(acute flares|475 μmol/l <sUA <595 μmol/l)	0.1085	β (304.4738, 2501.7361)	0.0973	0.1203	[18]
P(acute flares | sUA >595 μmol/l)	0.1161	β (301.9822, 2299.0704)	0.1041	0.1287	[18]
Mortality[a]		Assumed fixed as based on entire population			[32]
Mortality: SJS/TEN	0.2652	β (122, 338)	0.2259	0.3065	[6]
Mortality: DRESS	0.1000	β (13.73, 123.57)	0.0558	0.1552	[7]
Utilities					
*Gout with sUA <360 μmol/l[a]	0.7463	1-β (98.9914, 291.1993)	0.7020	0.7882	[18]
*Gout with 360 μmol/l <sUA <475 μmol/l[a]	0.7120	1-β (121.7288,300.9406)	0.6680	0.7541	[18]

(continued)

Table 1 Continued

Parameter	Mean	Distribution for probabilistic sensitivity analysis	Univariate sensitivity analysis		Reference
			Lower range	Upper range	
*Gout with 475 μmol/l <sUA <595μmol/l[a]	0.6777	1-β (145.1274,305.1592)	0.6339	0.7200	[18]
*Gout with sUA >595 μmol/l[a]	0.6435	1-β (168.6184, 304.3645)	0.5998	0.6860	[18]
Disutility: Gout flare	0.0097	β (15.8351, 1616.6494)	0.0055	0.0150	[18]
Disutility: SJS/TEN—acute	0.1400	γ (3.7867, 0.1901)	0.1869	1.6054	[33]
Disutility: SJS/TEN—long term	0.1149	γ (0.4423, 0.2597)	0.0000	0.6102	[34]
Disutility: DRESS—acute	0.1430	γ (0.9086, 0.1574)	0.0026	0.0121	[35]
Disutility: DRESS—long term	0.1149	γ (0.4423, 0.2597)	0.0000	0.6102	[34]
Resource use and costs					
Cost: Gout flare	321.62	γ (16, 20.1011)	183.83	497.31	[18]
Cost: Gout maintenance	97.40	γ (16, 6.0874)	55.67	150.60	[18]
Cost: Allopurinol 300 mg	3.77	Fixed	3.41	4.15	[26]
Cost: Febuxostat 80 mg	79.17	Fixed	71.60	87.11	[26]
Cost: Colchicine 1 mg (500 μg BID)	65.92	Fixed	59.62	72.54	[26]
Cost: SJS/TEN—acute	31 232.00	γ (1.18, 25 262.51)	1626.72	103 207.86	[36]
Cost: SJS/TEN—long term	140.00	γ (3.84, 42.17)	0.00	280.00	Expert opinion
Cost: DRESS—acute	£11 209.03	γ (7.44, 1507.13)	£4658.78	£20 585.50	[36]
Cost of *HLA-B*58* screen	54.29	Fixed	10.00	90.00	[36]
Cost of *HLA-B*58:01*	94.91	Fixed	30.00	150.00	[36]

[a]Tested simultaneously as utility of gout in univariate sensitivity analysis to preserve natural ordering. BID: twice a day; DRESS: drug reaction with eosinophilia and symptomatic symptoms; P: probability; RR: risk ratio; SJS: Stevens-Johnson syndrome; sUA: serum uric acid level; TEN: toxic epidermal necrolysis.

The probability of experiencing a flare during prophylaxis was taken from a pooled analysis of 8-week data from the FACT [29], APEX [30] and CONFIRMS trials [31] for allopurinol; and from a Cochrane review for febuxostat [28]. For subsequent model cycles, and for patients who were not prescribed urate lowering treatment, the probability of flares was determined by sUA level, as in Beard *et al*. [18].

Prevalence of allopurinol-induced SJS, TEN or DRESS

With a background population incidence of SJS/TEN of between 0.4 and 6 persons per million per year [15], and a risk ratio for allopurinol-induced SJS/TEN within the first 2 of initiation of 52 [19], the incidence of allopurinol-induced SJS/TEN was calculated as being between 0.2 and 3 cases per 10 000 patients. Within the model we use a mean point estimate of 1.6 cases per 10 000 patients. Data for DRESS were taken from a study of 1835 patients who were prescribed allopurinol, while monitored in a drug surveillance programme [37].

Association between *HLA-B*58:01* and allopurinol-induced SJS, TEN or DRESS

The systematic review by Somkura *et al*. [8] was updated using PubMed (from inception up until August 2016) using the search terms (HLA-B OR Human leucocyte antigen) AND allopurinol AND (Stevens Johnson Syndrome OR Toxic Epidermal Necrolysis OR Drug Reaction with Eosinophilia and Systematic Symptoms OR Drug Induced Hypersensitivity Syndrome OR Hypersensitivity Syndrome OR Allopurinol Hypersensitivity Syndrome) or their acronyms. Search results were cross-referenced against the allele frequencies database of studies of the association between *HLA-B*58:01* and allopurinol-induced ADR [9]. Studies were eligible for meta-analysis if they included an allopurinol tolerant control.

Meta-analysis was conducted using the metandi hierarchical logistic regression package in STATA (version 13; StataCorp LP, College Station, TX, USA) [38] to determine the pooled sensitivity and specificity of the presence of *HLA-B*58:01* in predicting allopurinol-induced SJS, TEN and DRESS.

Thirteen articles qualified for the meta-analysis (supplementary Table S1, available at *Rheumatology* Online). The pooled sensitivity of the 13 SJS/TEN studies was 0.95 (95% CI: 0.90, 0.97), with specificity 0.88 (95% CI: 0.84, 0.91). Meta-analysis of data from 10 DRESS studies resulted in a pooled sensitivity of 0.93 (95% CI: 0.84, 0.98) and specificity 0.85 (95% CI: 0.65, 0.94).

Based on the prevalence of allopurinol-induced SJS/TEN and DRESS, the positive predictive value of genotyping for SJS/TEN is 0.0013, whilst the negative predictive value of genotyping for SJS/TEN is 1.000. The corresponding values for DRESS are 0.0067 and 0.9999, respectively.

Allele prevalence

Pooled data for European populations (not restricted by ethnicity) resulted in an allele prevalence of 1.13% (95% CI: 1.08%, 1.19%) [9].

Health state utilities

There is limited evidence linking health state utility with sUA levels or incidence of flares [39]. To date, all EQ-5D data reported in published economic evaluations have been sourced from an unpublished study of 417 patients from the UK, Germany and France [4, 18]. In the absence of alternative data, we assumed the same relationship of health utility and sUA, with an additional decrement in utility of 0.0097 applied for episodes of acute flares [18].

Utility decrements corresponding to SJS/TEN and DRESS were assigned as for severe burns [33] and sepsis [35], respectively, consistent with other economic evaluations [17, 36, 40]. Longer term disutilities to capture long term sequelae for SJS, TEN and DRESS (applied to the model from 3 months post-ADR onwards) were taken from patient-level data for survivors of TEN [34].

Mortality

All-cause mortality was taken from UK life tables [32], adjusted by age and gender, while 3-month mortality for SJS/TEN and for DRESS were modelled at 26.5% (95% CI: 18%, 24%) [6] and 10% (95% CI: 5%, 15%) [7], respectively.

Costs

The total cost of gout maintenance treatment (£97.40 for 3 months) included consultation with General Practitioner, diagnostic tests (including sUA, serum creatinine and renal function), procedures (X-rays and joint aspiration) and hospitalization due to complications of gout such as urinary tract infections or renal stones [18]. The total cost of flare management (£321.62 for the immediate treatment and management of an acute flare) included the costs of inpatient hospitalization and outpatient clinic visits. The cost of allopurinol, febuxostat and colchicine were based on daily doses of 300 mg (titrated over the course of the first cycle), 80 and 1 mg, respectively [26].

The costs of the acute management of SJS/TEN and DRESS reactions were based on a previous economic evaluation [36], in which data on healthcare resource use (e.g. treatments, procedures, length of hospitalization according to intensity of care) were identified from a systematic review of the literature, and costed using NHS unit costs. We found no evidence for the cost of long term management of SJS/TEN and so assumed that patients would require follow-up consultant appointments, which were costed based on 1 h per annum. We further assumed there would be no cost incurred for managing sequelae of DRESS. The cost of genotyping was based on a two-stage process: an initial screen for *HLA-B*58* (£54.29) and, in patients who test positive, a second high resolution test for the specific *HLA-A*58:01* allele (£94.91) [36].

Analysis

Costs and QALYs were summed for genotyping prior to initiation of the urate lowering therapy, and for standard care (prescription of allopurinol without genotyping). The incremental cost-effectiveness ratio (ICER) was calculated as:

$$\text{ICER} = \frac{\text{Cost}_{\text{with test}} - \text{Cost}_{\text{standard care: no test}}}{\text{Outcome}_{\text{with test}} - \text{Outcome}_{\text{standard care: no test}}}$$

The economic evaluation was analysed in Microsoft Excel 2013, and reported according to the Consolidated Health Economic Evaluation Reporting Standards [41].

Sensitivity analysis

Parameter uncertainty was assessed by varying each parameter within its 95% CI or, if unavailable, within a plausible range which, in the case of costs, was based on a standard deviation of 25% of the mean (Table 1).

A probabilistic sensitivity analysis was performed using a Monte Carlo simulation with 10 000 replications, and a cost-effectiveness acceptability curve constructed to depict the probability of genotyping being cost-effective for a range of cost-effectiveness thresholds [42].

Scenario analysis

A scenario reflecting a single stage testing process was considered, at a cost of £20 per test. In order to simulate future price reduction of febuxostat, as may result following patent expiry, we explored the impact of equating the cost of febuxostat to that of allopurinol. We also present results from the first 6 months, corresponding with the time period where adverse events are most likely to occur.

We developed a scenario analysis that considered the case where patients experiencing SJS/TEN or DRESS with either allopurinol of febuxostat are treated symptomatically, which may reflect patients' reluctance to take further medicines following a serious ADR [43].

We also assessed alternative scenarios for patients who test positive for *HLA-B*58:01*. Firstly, we considered such patients to be treated symptomatically, without maintenance uric acid lowering treatment, which may reflect a patient preference to discontinue treatment [44]. Secondly, we considered the scenario in which allopurinol would continue to be prescribed but that patients would be monitored closely. In this scenario, we assumed monitoring would also take place in patients prescribed febuxostat or symptomatic treatment, following experience of SJS/TEN or DRESS. Whilst the incidence of SJS/TEN or DRESS will not be affected by increased monitoring, early discontinuation of causative drug has been shown to improve mortality outcomes, with odds ratio 0.69/day [45]. The cost of the monitoring service was based on 20 min of a pharmacist's time, costed at £71/h, to allow for additional information at initiation and two follow-up phone calls during the first 6 months [46].

A scenario analysis that limits testing to patients with chronic renal insufficiency was assessed given this being an independent risk factor for SJS/TEN and DRESS in patients prescribed allopurinol (relative risk compared with no chronic renal insufficiency 3.79; 95% CI: 2.43, 5.92) [30]. Patients with chronic renal insufficiency (eGFR 15–29 ml/min/1.73 m^2) have a standardized mortality ratio of 3.2 (95% CI: 3.1, 3.4) [25], and SJS/TEN is associated with increased mortality in this patient group (67% of patients experiencing SJS/TEN do not survive the ADR) [30]. The increased prevalence of SJS/TEN and associated mortality were modelled alongside reduced dose of allopurinol (100 mg/day) and reduce dose of colchicine (0.5 mg/day) as recommended for this population [26].

As being female is associated with a higher risk of allopurinol-induced SJS/TEN or DRESS (OR = 1.45; 95% CI: 1.35, 1.56) [9, 47], and SJS/TEN and DRESS mortality is higher in females (OR = 1.63; 95% CI: 1.28, 2.08) [47], we conducted an analysis for a female population subgroup, aged 62 years.

While the primary analysis is for a European population, the population of the UK is ethnically diverse. We conducted an analysis that considered an increased prevalence of *HLA-B*58:01*, based on a pooled analysis of populations of Asian ethnic origin, at 4.24% [9]. A further analysis was considered for the population with greatest prevalence of *HLA-B*58:01*, at 17% (the China Guangdong Province Meizhou Han population) [9].

Finally, as the long term impact of alternative treatments and the long term consequences of SJS/TEN or DRESS will have a greater lifetime impact on younger populations, we tested the cost-effectiveness of testing in a population of 35-year-old males.

Results

The modelled rate of ADRs in the test group was 0.95 [95% central range (CR): 0.16, 3.04] per 10 000 patients, compared with 1.83 (95% CR: 0.40, 6.00) in the standard care group. The number needed to screen in order to prevent one ADR (either SJS/TEN or DRESS) is 11 286 (95% CR: 2573, 53 594).

There is a small, but significant, incremental cost of £103 (95% CR: £98, £106) associated with testing (Table 2). Cost differences are mainly attributable to drug costs and the cost of genotyping. There is also a very small QALY gain from testing, of 0.0023 (95% CR: −0.0006, 0.0055), but this is not significant. QALY gains predominantly derive from better management of gout as febuxostat is more efficacious than allopurinol. The resulting ICER for *HLA-B*58:01* genotyping was £44 954 per QALY gained.

Parameter and structural sensitivity analysis

A tornado plot illustrating the sensitivity of the ICER to the 10 most influential parameters is shown in Fig. 2. Univariately, the efficacy of febuxostat (risk ratio for achieving sUA <360 μmol/l *vs* allopurinol) and the cost of genotyping were most influential. The ICER was stable to variation in all other parameters within their 95% CI.

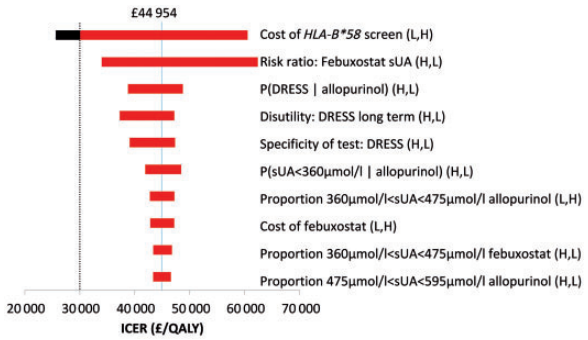
Figure 3 presents the cost-effectiveness acceptability curve for the base case analysis, which indicates that

Table 2 Results of the base-case analysis

Scenario	Test		Standard care		Incremental	
	Cost	QALYs	Costs	QALYs	Costs	QALYs
Gout management	£5597	10.3400	£5596	10.3378	£0.06	0.0022
Gout flare management (prophylaxis)	£45.26	−0.0003	£45.10	−0.0003	£0.16	0.0000
Gout flare management (non-prophylaxis)	£1741	−0.0131	£1742	−0.0131	−£0.82	0.0000
Treatment of SJS/TEN and DRESS	£1.27	−0.000004	£2.53	−0.000012	−£1.26	0.0000
Managing sequelae of SJS/TEN and DRESS	£0.06	−0.0001	£0.14	−0.0003	−£0.08	0.0001
Genotyping	£55.50		£0		£55.50	
Drug cost	£333.79		£284.30		£49.49	
Total	£7773	10.3264	£7671	10.3241	£103.05	0.0023

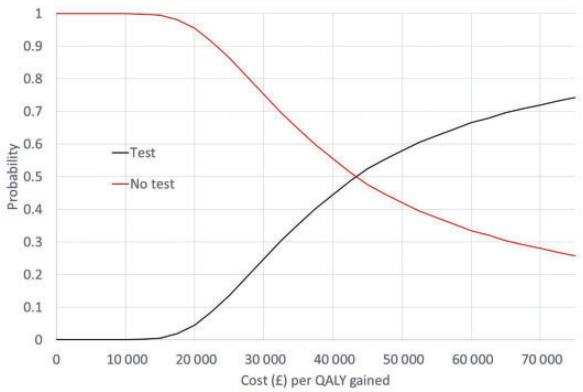
DRESS: drug reaction with eosinophilia and symptomatic symptoms; QALY: quality-adjusted life-year; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis.

Fig. 2 Tornado plot illustrating univariate sensitivity analysis



(L,H) and (H,L) indicate whether the range tested is displayed as low–high or high–low, respectively. The vertical line at £44 954 per QALY gained represents the ICER corresponding to the base case analysis. ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life-year; sUA: serum uric acid level.

Fig. 3 Cost effectiveness acceptability curve



QALY: quality-adjusted life-year.

the probabilities of genotyping being cost effective at ceiling ratios of £20 000 and £30 000 per QALY are 0.05 and 0.25, respectively.

Scenario analyses (Table 3) indicate testing to be cost-effective within populations with a higher prevalence of *HLA-B*58:01* (at £27 218 and £22 359 per QALY gained, for 4.24% and 17% prevalence, respectively) where the number needed to screen to prevent one ADR reduces to 3018 and 753, and when the cost of febuxostat is reduced to that of allopurinol, resulting in an ICER of £23 679 per QALY gained. A less expensive, single-stage test reduces the ICER to £29 469 per QALY gained. In the case of both reduced price febuxostat and cheaper testing, the ICER is £8195 per QALY gained.

Blanket prescription of allopurinol with only symptomatic treatment following ADR resulted in a reduction in both costs and QALYs. For other scenarios, and alternative modelling assumptions, ICERs remained higher than £30 000 per QALY. While the number needed to screen to prevent one case of SJS/TEN in patients with chronic renal insufficiency reduced to 2964, testing remained not cost-effective at £38 478 per QALY gained. Based on a 12-month time horizon of analysis, the QALY gain, being almost solely attributable to the reduction in cases of SJS/TEN and DRESS, is very small, which inflates the ICER.

Discussion

Our model suggests that from a UK NHS perspective, routine genotyping for *HLA-B*58:01* is not cost-effective for preventing SJS/TEN and DRESS associated with allopurinol in patients with gout. The small QALY gain, equivalent to less than one quality-adjusted day, is commonplace in pharmacogenetic testing due to the low allele prevalence and rarity of the adverse event leading to a low positive predictive value [48]. In scenario analyses, genotyping was modelled to be cost-effective when the price of testing reduced to $\leqslant$£21 per patient, or when the cost of febuxostat is reduced, such as might be expected once available generically, expected in 2019. The model was

Table 3 Results of scenario analyses

Scenario	Incremental cost (per patient)	Incremental QALY (per patient)	Number needed to screen to prevent one ADR	ICER (Cost/QALY)
Base case	£103.05	0.0023	11 286	£44 954
Results at 6 months	£56.81	0.0001	11 286	£706 624
35-year-old male	£128.68	0.0035	11 286	£36 571
62-year-old female	£107.06	0.0026	10 437	£41 176
Chronic renal insufficiency[a]	£84.46	0.0022	2964	£38 478
Prevalence of *HLA-B*58:01* 4.24%	£233.34	0.0086	3018	£27 218
Prevalence of *HLA-B*58:01* 17%	£768.55	0.0344	753	£22 359
Set comparator ULA cost equal to allopurinol[b]	£54.28	0.0023	11 286	£23 679
Single stage test, cost £20	£67.55	0.0023	11 286	£29 469
All prescribed allopurinol. No ULA in case of ADR	−£0.72	−0.0001	[c]	£11 081[d]
Test negative: Allopurinol; Test positive: Febuxostat; No ULA in case of ADR	£102.69	0.0023	11 284	£45 456
Test negative: Allopurinol; Test positive: No ULA; No ULA in case of ADR	£51.18	−0.0024	11 003	Dominated
Test negative: Allopurinol; Test positive: Allopurinol with increased monitoring; Febuxostat in case of ADR	£55.82	0.0000	[c]	£1 783 994

[a]Chronic renal insufficiency: SJS/TEN PPV 0.0048; SJS/TEN NPV 1.0000; DRESS PPV 0.0251; DRESS NPV 0.9997. [b]Colchicine maintained for 6 months due to prophylaxis flare rate. [c]In excess of the number of people with gout in the UK. [d]Less costly and less effective. ADR: adverse drug reaction; ICER: incremental cost effectiveness ratio; NPV: negative predictive value; PPV: positive predictive value; QALY: quality-adjusted life year; ULA: urate lowering agent.

robust to the alternative assumption of no uric acid lowering treatment being prescribed following a serious ADR, which may reflect patient or prescriber preference [43].

We are aware of three existing economic evaluations of *HLA-B*58:01* screening for preventing allopurinol-induced SCAR, with mixed results of cost-effectiveness [15–17]. Differences among these studies can be attributed to differences in populations but also methodological limitations that are addressed in our analysis.

Firstly, our analysis has strength in the use of febuxostat as a realistic and licensed comparator to allopurinol for a UK setting. Of the previously conducted economic evaluations, only Park [16] considered febuxostat as a comparator; both other studies considered probenecid as the comparator [15, 17], which has very limited use in the UK.

Secondly, previous economic evaluations made no consideration of the relative effectiveness of urate lowering drugs, and focused exclusively on differences in the rates of SCAR. The Thai analysis, for instance, assumed a single health utility applied to all patients regardless of treatment received [15]. This represents a major limitation, as febuxostat may be more effective than allopurinol in lowering serum urate, if not in reducing the incidence of gout flares or tophus area [40]. By adopting a lifetime horizon of analysis that captured the differences in efficacy and costs between treatments, our analysis reduces this bias while also taking fully into account the long term sequelae of SJS/TEN and DRESS.

Only one previous economic evaluation has considered hypersensitivity reactions other than SJS/TEN [17], and we are the first to consider SJS/TEN and DRESS separately.

Our analysis also benefited from having modelled a number of potential patient populations, to reflect different clinical circumstances where genotyping may be cost-effective, as well as different scenarios of drug sequences in patients who experience ADRs and future decreases in the cost of testing and febuxostat.

As with any economic model, however, we were reliant on disparate sources of evidence and some assumptions were necessary. Firstly, we relied on unpublished data on utilities in gout. Alternative published data of EQ-5 D utilities in 110 patients did not present utility by drug, disease severity or response to treatment, and were therefore unsuitable for populating the model [49]. However the mean (S.D.) utility value of 0.74 (0.23) is consistent with the data used in our analysis.

Secondly, our analysis did not capture any adverse events other than SJS/TEN or DRESS, which may have implications, especially in chronic renal populations. Neither were other common comorbidities, such as cardiovascular disease and diabetes, taken into account explicitly. However, with the assumption that the populations from which costs and utilities were sourced were representative of a general gout population, such comorbidities would have been captured implicitly.

Thirdly, the scenario representing patients with chronic renal insufficiency did not account for costs or QALYs associated with the condition, but only the impact of the condition on SJS/TEN and DRESS, mortality and prescription costs. Moreover, there was no evidence as to whether the rate of SJS/TEN or DRESS in febuxostat treated patients with chronic renal insufficiency would be any higher than in the general population.

Fourthly, in the absence of data, we assumed that the probability of an increase in flares during the prophylaxis period is independent of the probability of achieving sUA <360 μmol/l.

Finally, we assumed that sUA remains constant after 12 weeks provided that treatment does not change. This is consistent with other economic evaluations [17, 18], and with results from the EXCEL study [20], but requires patients to be fully adherent, which may not be the case in practice [44]. The EXCEL study noted that after 24 months, 76% of patients prescribed febuxostat remained on treatment, while only 40% of patients persisted with allopurinol [20].

In conclusion, our analysis suggests that routine, prospective genotyping for *HLA-B*58:01* prior to the prescription of allopurinol for gout is not cost-effective in a UK NHS setting. There are, however, subpopulations where testing is more likely to be cost effective, including patients with chronic renal insufficiency, and populations with a higher *HLA-B*58:01* prevalence. Testing is expected to become cost-effective with reductions in the cost of genotyping, and with the future availability of cheaper, generic febuxostat.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

1 Roddy E, Mallen CD, Doherty M. Gout. BMJ 2013;347:f5648.

2 Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet 2016;388:2039–52.

3 Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Ann Rheum Dis 2015;74:661–7.

4 Annemans L, Spaepen E, Gaskin M *et al*. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000-2005. Ann Rheum Dis 2008;67:960–6.

5 Kim SC, Newcomb C, Margolios D, Roy J, Hennessy S. Severe cutaneous reactions requiring hospitalization in allopurinol initiators: a population-based cohort study. Arthritis Care Res 2013;66:578–84.

6 Sekula P, Dunant A, Mockenhaupt M *et al*. Comprehensive survival analysis of a cohort of patients with Stevens–Johnson syndrome and toxic epidermal necrolysis. J Invest Dermatol 2013;133:1197–204.

7 Turney R, Skittrall JP, Donovan J, Agranoff D. Drug Reaction, Eosinophilia and Systemic Symptoms (DRESS) syndrome secondary to allopurinol with early lymphadenopathy and symptom relapse. BMJ Case Rep 2015;2015:bcr2015211222.

8 Somkura R, Eickman EE, Saokaew S, Lohitnavy M, Chaiyakunapruk N. Association of HLA-B*5801 allele and allopurinol induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. BMC Medical Genet 2011;12:118–28.

9 Allele Frequencies Database. www.allelefrequencies.net (16 March 2016, date last accessed).

10 Stamp LK, Day RO, Yun J. Allopurinol hypersensitivity: investigating the cause and minimizing the risk. Nat Rev Rheumatol 2016;12:235–42.

11 Drug label annotations. https://www.pharmgkb.org/view/drug-labels.do (4 May 2016, date last accessed).

12 Khanna D, FitzGerald JD, Khanna PP *et al*. 2012 American College of Rheumatology guidelines for management of gout. Part I: Systematic non-pharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res 2012;64:1431–46.

13 Ko TM, Tsai CY, Chen SY. Use of HLA-B*58:01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: national prospective cohort study. BMJ 2015;351:h4848.

14 Jung JW, Kim DK, Park HW *et al*. An effective strategy to prevent allopurinol-induced hypersensitivity by HLA typing. Genet Med 2015;17:807–14.

15 Saokaew S, Tassaneeyakul W, Maenthaisong R, Chaiyakunapruk N. Cost-effectiveness analysis of HLA-B*5801 testing in preventing allopurinol-induced SJS/TEN in Thai population. PLoS One 2014;9:e94294.

16 Park DJ, Kang JH, Lee JW *et al*. Cost-effectiveness analysis of HLA-B5801 genotyping in the treatment of gout patients with chronic renal insufficiency in Korea. Arthritis Care Res 2015;67:280–7.

17 Dong D, Tan-Koi WC, Teng GG, Finkelstein E, Sung C. Cost-effectiveness analysis of genotyping for HLA-B*5801 and an enhanced safety program in gout patients starting allopurinol in Singapore. Pharmacogenomics 2015;16:1781–93.

18 Beard S, von Scheele BG, Nuki G, Pearson IV. Cost-effectiveness of febuxostat in chronic gout. Eur J Health Econ 2014;15:453–63.

19 Roujeau JC, Kelly JP, Naldi L *et al*. Medication use and the risk of Stevens-Johnson Syndrome or toxic epidermal necrolysis. N Engl J Med 1995;333:1600–7.

20 Becker MA, Schumacher HR, MacDonald PA, Lloyd E, Lademacher C. Clinical efficacy and safety of successful long term urate lowering with febuxostat or allopurinol in subjects with gout. J Rheumatol 2009;36:1273–82.

21 Chohan S. Safety and efficacy of febuxostat treatment in subjects with gout and severe allopurinol adverse reactions. J Rhuematol 2011;38:1957–9.

22 Chung WH, Pan RY, Chu MT *et al*. Oxypurinol-specific T cells possess preferential TCR clonotypes and express granulysin in allopurinol-induced severe cutaneous adverse reactions. J Invest Dermatol 2015;135:2237–48.

23 Febuxostat Summary of Product Characteristics. http://www.medicines.org.uk/emc/medicine/22830 (16 March 2016, date last accessed).

24 Zhang W, Doherty M, Bardin T *et al*. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR standing committee for international clinical studies including therapeutics (ESCISIT). Ann Rheum Dis 2006;65:1312–24.

25 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:3728–35.

26 Joint Formulary Committee. British National Formulary, 66th edn. London: Royal Pharmaceutical Society of Great Britain, 2014: 701–3.

27 Seth R, Kydd ASR, Buchbinder R, Bombadier C, Edwards CJ. Allopurinol for chronic gout. Cochrane Database Syst Rev 2014;10:CD006077.

28 Tayar JH, Lopez-Olivo MA, Suarez-Almazor ME. Febuxostat for treating chronic gout. Cochrane Database Syst Rev 2012;11:CD008653.

29 Becker MA, Schumacher HR, Wortmann RL *et al*. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005;353:2450–61.

30 Schumacher HR, Becker MA, Wortmann RL *et al*. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-bind, parallel-group trial. Arthritis Rheum 2008;59:1540–8.

31 Becker MA, Schumacher HR, Espinoza LR *et al*. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyeruricemia of gout: the CONFIRMS trial. Arthritis Res Ther 2010;12:R63.

32 Human Mortality Database. www.mortality.org (20 January 2016, date last accessed).

33 Öster C, Willebrand M, Dyster-Aas J, Kildal M, Ekselius L. Validation of the EQ-5D questionnaire in burn injured adults. Burns 2009;35:723–32.

34 Haber J, Hopman W, Gomez M, Cartotto R. Late outcomes in adult survivors of toxic epidermal necrolysis after treatment in a burn center. J Burn Care Rehabil 2005;26:33–41.

35 Hofhuis JG, Spronk PE, van Stel HF *et al*. The impact of severe sepsis on health-related quality of life: A long-term follow-up study. Anesth Analg 2008;107:1957–64.

36 Plumpton CO, Yip VL, Alfirevic A *et al*. Cost-effectiveness of screening for HLA-A*31:01 prior to initiation of carbamazepine in epilepsy. Epilepsia 2015;56:556–63.

37 McInnes GT, Lawson DH, Jick H. Acute adverse reactions attributed to allopurinol in hospitalised patients. Ann Rheum Dis 1981;40:245–9.

38 Harbord, RM, Whiting, P. metandi: Meta-analysis of diagnostic accuracy using hierarchical logistic regression. Stata J 2009;9:211–29.

39 Rai SK, Burns LC, De Vera MA *et al*. The economic burden of gout: A systematic review. Semin Arthritis Rheum 2015;45:75–80.

40 Dong D, Sung C, Finkelstein EA. Cost-effectiveness of HLA-B*1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore. Neurology 2012;79:1259–67.

41 Husereau D, Drummond M, Petrou S *et al*. ISPOR health economic evaluation publication guidelines-CHEERS good reporting practices task force Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. Value Health 2013;16:231–50.

42 Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Econ 2001;10:779–87.

43 Butt TF, Cox AR, Lewis H, Ferner RE. Patient experiences of serious adverse drug reactions and their attitudes to medicines: a qualitative study of survivors of Stevens-Johnson syndrome and toxic epidermal necrolysis in the UK. Drug Saf 2011;34:319–28.

44 Harrold LR, Andrade SE, Briesacher BA *et al*. Adherence with urate-lowering therapies for the treatment of gout. Arthritis Res Ther 2009;11:R46.

45 Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? Arch Dermatol 2000;136:323–7.

46 Curtis L. Unit Costs of Health & Social Care 2015. Canterbury: Personal Social Services Research Unit, University of Kent, 2015.

47 Yang CY, Chen CH, Deng ST *et al*. Allopurinol use and risk of fatal hypersensitivity reactions: A nationwide population-based study in Taiwan. JAMA Intern Med 2015;175:1550–7.

48 Veenstra DL. The value of routine pharmacogenomic screening—Are we there yet? A perspective on the costs and benefits of routine screening—shouldn't everyone have this done? Clin Pharmacol Ther 2016;99:164–6.

49 Spaetgens B, Wijnands JMA, van Durme C, van der Linden S, Boonen A. Cost of illness and determinants of costs among patients with gout. J Rheumatol 2015;42:335–44.