Pharmacogenetic testing prior to carbamazepine treatment of epilepsy: 1 patients' and physicians' preferences for testing and service delivery
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1   **Title:** Pharmacogenetic testing prior to carbamazepine treatment of epilepsy: patients' and

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24   **Summary**

25   **Aim**: Pharmacogenetic studies have identified the presence of the *HLA-A*31:01* allele as a predictor

26   of cutaneous adverse drugs reactions (ADRs) to carbamazepine. This study aimed to ascertain the

27   preferences of patients and clinicians to inform carbamazepine pharmacogenetic testing services.

28   **Methods**: Attributes of importance to people with epilepsy and neurologists were identified through

29   interviews and from published sources. Discrete choice experiments (DCEs) were conducted in 82

30   people with epilepsy and 83 neurologists. Random-effects logit regression models were used to

31   determine the importance of the attributes and direction of effect.

32   **Results**: In the patient DCE, all attributes (seizure remission, reduction in seizure frequency, memory

33   problems, skin rash and rare, severe ADRs) were significant. The estimated utility of testing was

34   greater, at 0.52 (95% CI, 0.19 to 1.00) than not testing at 0.33 (95% CI, -0.07 to 0.81). In the physician

35   DCE, cost, inclusion in the British National Formulary, coverage, negative predictive value (NPV), and

36   positive predictive value (PPV) were significant. Marginal rates of substitution indicated that

37   neurologists were willing to pay £5.87 for a 1 percentage point increase in NPV and £3.99 for a 1

38   percentage point increase in PPV.

39   **Conclusion**: The inclusion of both patients' and clinicians' perspectives represents an important

40   contribution to the understanding of preferences towards pharmacogenetic testing prior to initiating

41   carbamazepine. Both groups identified different attributes but had generally consistent

42   preferences. Patients' acceptance of a decrease in treatment benefit for a reduced chance of severe

43   ADRs adds support for the implementation of *HLA-A*31:01* testing in routine practice.

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46   **What is known about this subject:**

47   • Carbamazepine is associated with severe, immune-mediated adverse drug reactions that may be

48   predicted, and potentially avoided, by testing for human leukocyte antigen alleles

49   • There is presently no evidence on the preferences of patients with epilepsy or neurologists

50   towards pharmacogenetic testing prior to carbamazepine treatment

51   **What this study adds:**

52   • Based on discrete choice experiments, patients were willing to accept a reduced chance of 1-

53   year remission from seizures for a reduction in adverse drug reactions

54   • Neurologists' preference for testing was sensitive to the cost of the test, but they were willing to

55   pay for a modest increase in negative predictive value

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Introduction

Carbamazepine is used widely as a first-line treatment for focal onset seizures, and has proven benefits in terms of time to achieving 12-month remission [1,2]. However, it is associated with common adverse drug reactions (ADRs) [3] and more serious, immune-mediated ADRs, including cutaneous hypersensitivity reactions such as Drug Induced Hypersensitivity Syndrome (DIHS), Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). The estimated incidence of SJS-TEN is 1 to 6 per 10,000 persons exposed to carbamazepine with TEN being associated with mortality of up to 30% [4].

Pharmacogenetic association studies have identified significant genetic predictors of cutaneous ADRs associated with carbamazepine. While rare in European populations, the *HLA-B*15:02* allele is a significant predictor of SJS-TEN in people of Han-Chinese descent [5], and testing significantly reduces the rate of SJS-TEN [6]. Recommendations from regulators have consequently led to increased use of *HLA-B*15:02* testing of people of Han-Chinese, Thai and other Asian origin in East Asia.

In European populations, the *HLA-A*31:01* allele is a significant predictor of the full spectrum of carbamazepine-induced hypersensitivity ADRs [7], the risk being 26% in carriers of the allele and 3.8% in non-carriers. Based on the 10% prevalence of mild carbamazepine-induced cutaneous ADRs (maculopapular exanthema) in people of European descent [1], 39 people would need to be screened to prevent one carbamazepine-induced ADR [7]. However testing for *HLA-A*31:01*, which has a prevalence of 2 to 5% in European populations, has yet to gain mainstream acceptance in Western countries. As for any new innovation, uptake will be dependent on many factors, not least patients' acceptance, and preferences for harm reduction versus benefit maximisation; and prescribers' considerations of diagnostic value, clinical utility and cost, among other factors [8].

Discrete choice experiments (DCEs) are a method for measuring respondents' stated preference for healthcare interventions or services [9]. In DCEs, respondents are asked to choose their preferred

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82   alternative from a set of hypothetical (but realistic) alternatives. The method allows for the

83   estimation of the relative importance of different aspects of care, assessment of any trade-offs

84   between these aspects, and of respondents' total satisfaction (utility) associated with the

85   intervention or service under consideration [9,10]. DCEs have been used previously to elicit

86   preferences for antiepileptic drugs (AEDs) [11,12] and for the delivery of pharmacogenetic testing

87   services [13]. The latter revealed differences in patient and prescriber preferences, with patients

88   demanding accurate and timely information regarding why testing was necessary and what the test

89   results meant, while health-care professionals focussed more on the predictive accuracy and waiting

90   time for a test result [13].

91   In the present study, we aimed to ascertain the preferences of patients with epilepsy and

92   neurologists when considering testing for *HLA-A*31:01* prior to prescribing carbamazepine.

93   Specifically, we estimated patients' threshold at which the incidence of serious ADR would make

94   testing worthwhile and neurologists' willingness to pay for testing. The results of this study may

95   inform the delivery of pharmacogenetic testing services.

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97 **Methods**

98 *Overview*

99 We identified attributes that patients with epilepsy and neurologists considered important in their

100 respective consideration of pharmacogenetic testing prior to starting treatment with

101 carbamazepine. Levels for each attribute were derived from appropriate sources of clinical

102 evidence. Separate DCEs were designed and administered to samples of patients with epilepsy and

103 neurologists from across the UK.

104 *Participants and administration*

105 Adults aged 18 or over and who self-reported as being diagnosed with epilepsy by a doctor were

106 eligible. Participants were not rewarded for their time but were informed of the potential benefits

107 and risks to them, and had to consent before taking part. Recruitment was facilitated by the UK

108 charity Epilepsy Action and included advertisements, articles and links using social media, members'

109 magazine, e-forums and newsletters, and website home page. An advertisement was placed in the

110 local press and posters displayed in hospital clinics. The questionnaire was made available via a link

111 to an anonymous online service (Snap Surveys, London, UK) between June and October 2013. Target

112 sample size was 63 completed DCE responses, based on each main effect level of interest being

113 represented across the design at least 500 times [14]. Ethical approval was gained from the NHS

114 National Research Ethics Service (reference 11/NW/0191).

115 Adult and paediatric neurologists registered in the UK were recruited via the International League

116 Against Epilepsy and the Association of British Neurologists. The questionnaire was made available

117 nationally via an anonymous online service (SurveyMonkey, Palo Alto, CA) between July and October

118 2012. The target sample size for the main effects analysis was 47 completed DCE responses [14].

119 *Attribute and level selection*

6

120 Attributes for the patient DCE were identified using semi-structured interviews with patients, focus

121 group with prescribers, and from published data. Patients (n=56) were recruited from three clinical

122 sites, and included 33 with established epilepsy (17 females, mean age 38 years) and 23 with a

123 recent (≤1 year) diagnosis of epilepsy (10 females, mean age 43 years). Forty-one patients were first

124 asked to list and rank attributes relating to the benefits, side-effects and life-impacts of treatment

125 for epilepsy. The second stage of the interviews was designed to explore the framing of risk and the

126 validity of risk communication. Fifteen patients participated in cognitive interviews to assess the

127 face validity of the DCE (presentation of attributes and levels) and were provided with show-cards

128 depicting risk in pictograms alongside a written explanation of the risk being illustrated.

129 Interviewers were given notes on how to explain risk. This exercise was repeated in the focus group

130 with prescribers (n=8), who were also asked to discuss the frequency and severity at which side-

131 effect became a 'clinically important adverse event' that would require a change in treatment.

132 Prescribers were also asked for feedback on the format of the patient DCE and the presentation of

133 attributes and levels. The final DCE of patients contained 5 attributes to represent remission of

134 seizures (the highest ranked benefit in the qualitative study), reduction in seizure frequency,

135 memory problems (the highest ranked side-effect in the qualitative study), skin rash, and rare or

136 uncommon severe ADRs (associated with carbamazepine) (Table 1). Appropriate levels for each

137 category were identified from published clinical data [1,7,15].

138   Insert Table 1 here

139 Attributes for the physician DCE were taken from Payne et al. [13], who identified cost, predictive

140 accuracy and result turnaround time as being important when considering pharmacogenetic tests;

141 and from structured individual interviews with neurologists (n=12) recruited from the North West of

142 England. Initial interviews involved a discussion of attributes that would be of potential importance

143 to neurologist when considering a pharmacogenetic test and included: cost, predictive accuracy,

144 turnaround time to result, coverage of test (severe ADRs only or severe and mild ADRs), inclusion in

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145   British National Formulary (BNF) [16], method of testing (blood, salivary swab), method of follow-up

146   and subsequent prescribing, location of testing and method of presentation of results ('raw data',

147   summarised interpretation).

148   A rating exercise was performed to identify the attributes of greatest importance. Subsequent

149   interviews with neurologists discussed the presentation of the attributes and identified relevant

150   levels. As this study targeted UK neurologists, cost was understood to be total cost to the National

151   Health Service (NHS), rather than cost to the patient or cost for a privately requested test. Although

152   there is no direct cost to the neurologist or patient, neurologists and physicians in general in the UK

153   are cognisant of the costs of medical interventions and this characteristic was confirmed by the

154   identification of the attribute as important in the interviews. Framing of the predictive attributes of

155   the pharmacogenetic test was discussed. The negative predictive value (NPV) and positive predictive

156   value (PPV) were understood and favoured by the neurologists compared to alternative methods of

157   presentation including sensitivity, specificity or 'risk of ADR following test'. The final attributes

158   presented in the DCE were: cost, time to result, inclusion in the BNF, coverage, NPV, and PPV (Table

159   1). Data from published sources [5,7], together with discussion in individual interviews with

160   neurologists and expert opinion led to identification of a range of plausible attribute levels.

161   *Experimental design*

162   Our qualitative findings did not reveal a common list of attributes that could be used to value both

163   physician and patient preferences for pharmacogenetic testing services. We therefore conducted

164   two separate DCEs that contained the most relevant and plausible attributes from both

165   perspectives.

166   In clinical practice, patients who test positive for the *HLA-A*31:01* allele would be prescribed an

167   alternative AED, which is likely to have a different benefit and harm profile. To reflect this, the DCE

168   asked patients to choose between two hypothetical medicines, from which we inferred their

8

169 preference for pharmacogenetic testing. The DCE used a fractional factorial design [18] and folded

170 into eight binary choices, one of which is presented as an example in Figure 1. The DCE was

171 administered as part of a larger survey containing 126 items in total and requiring an estimated 30

172 minutes for completion

173 A binary design was selected for the DCE of neurologists in order to include a choice of no testing,

174 which is aligned with current clinical practice. A fractional factorial design was selected from a design

175 catalogue to ensure orthogonality [18]. Sixteen choice scenarios were presented to respondents,

176 following the example shown in Figure 1.

177   Insert Figure 1 here

178 ***Analysis***

179 Random effects logit regression models were used to determine the importance of the attributes

180 and direction of effect. Marginal rates of substitution (MRS, the rate at which respondents were

181 willing to give up a unit change in one attribute in exchange for a unit change in another while

182 maintaining the same level of utility) were calculated using each attribute as the value attribute with

183 Bootstrapped confidence intervals calculated using 1,000 replications. All analyses were conducted

184 in STATA version 10 (StataCorp, College Station, TX). To test the validity of the patient DCE we

185 identified a potentially dominant choice in which medicine A was superior in all but one attribute

186 (higher chance of remission, lower risk of memory problems, mild rash and life-threatening ADR; but

187 a higher frequency of seizures). We assumed that people who selected the alternative (medicine B)

188 for this choice did not understand the task, and analysed the DCE with and without these

189 respondents by comparing the confidence intervals of all the coefficients in the regression to

190 ascertain if there were statistically significant differences.

191 Patients' utility was calculated by weighting the results of the regression against potential outcomes

192 of treatment with carbamazepine with or without pharmacogenetic testing. Clinical data [1,7,15]

9

193   were used to model the scenarios of testing (in which carriers of the *HLA-A*31:01* allele are

194   prescribed lamotrigine) and standard care (Table 2). The probability of test uptake was calculated as

195   the exponential of the utility for testing divided by the sum of the exponential of the utilities for

196   testing and not testing. We further calculated the threshold at which patients would prefer to be

197   tested, defined when the utility of testing is at least as much as the utility of standard treatment:

$$-\sum_{1}^{N} MRS_{attribute(N)} * \Delta_{attribute(N)} \leq \Delta_{sADR}$$

198   where, *MRS* is the ratio of beta coefficient for a given attribute divided by the beta coefficient for

199   severe ADRs (*sADR*), and $\Delta_{attribute}$ represents the actual difference in probabilities of occurrence of

200   attribute-defined events between a testing strategy and standard treatment. The trade-off between

201   the benefits and harms of interest provides the point of indifference from the patient's perspective

202   and therefore represents the threshold at which patients would choose to be tested.

203   Insert Table 2 here

204   *Scenario analyses*

205   While the base case focused on *HLA-A*31:01*, a scenario analysis was performed using the

206   characteristics of testing for *HLA-B*15:02*. This was based on a meta-analysis of the association with

207   SJS/TEN [19] and assumed a 10% allele prevalence, consistent with Asian populations [20].

208   A further exploratory analysis was conducted by identifying statistically significant subgroups based

209   on log likelihood ratio tests of base case 'restricted model' (all cases) and unrestricted models for

210   groups of n≥30 and assuming p<0.05 with Bonferroni correction.

211   For the DCE of neurologists, welfare estimates including total utility and probability of uptake were

212   calculated for various testing scenarios which represented: a less expensive test, higher PPV and

213   NPV, and a reduced time to test result. A test which costs £100, takes 4 days for the result, with PPV

214   26%, NPV 96%, predictive of both severe and mild ADRs but not included in the BNF was selected as

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215   being representative of current clinical practice associated with *HLA-A*31:01* testing. An assessment

216   of validity using a dominant choice set was not possible in the DCE of neurologists. Pharmacogenetic

217   testing for *HLA-A*31:01* is not currently mandatory and therefore selecting a single scenario where a

218   test should always or never be selected would not be appropriate in the context of a labelled DCE.

219   We defined non-traders as respondents always selecting one response (test or no test) and

220   examined the results of the regression with and without the inclusion of non-traders.

221

222   **Results**

223   *Patients' DCE*

224   Ninety-two people with epilepsy started the DCE, of which 82 (89%) completed the survey.

225   Respondents had a median age of 38 years and 61 (66%) were female (Table 3). Almost all patients

226   were taking AEDs (n=85, 99%) and 31 (36%) had experienced changes to their AED treatment in the

227   previous three months. Over a third of respondents (n=31, 36%) had previously taken

228   carbamazepine to treat epilepsy, of which one respondent reported a severe skin reaction requiring

229   hospitalisation and 10 (19%) had experienced rash of the upper body.

230   Insert Table 3 here

231   All 5 attributes were significant and in the expected direction and the overall goodness of fit of the

232   model was good (Table 4). Five patients failed to select the dominant choice, however as there were

233   no statistically significant differences between models by their inclusion or exclusion they were

234   retained in the base case analysis. Patients were willing to accept a reduction in the chance of 12-

235   month remission from seizures in exchange for a reduction in adverse events. Patients were willing

236   to reduce the chance of remission by: 0.58 percentage points (95% CI, 0.39 to 0.82) for a 1

237   percentage point reduction in skin rash; 3.2 percentage points (95% CI, 2.32 to 4.44) for a 1

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238   percentage point reduction in memory problems; and, 1.76 percentage points (95% CI, 1.21 to 2.54)

239   for a 0.001 percentage point reduction in the risk of a severe ADR.

240   Insert Table 4 here

241   *Utility model*

242   The estimated utility associated with testing for *HLA-A*31:01* was greater, at 0.52 (95% CI, 0.19 to

243   1.00) than not testing at 0.33 (95% CI, -0.07 to 0.81). Consequently the choice model estimated the

244   probability of test uptake at 55% (95% CI, 54 to 57) which would suggest that more patients would

245   choose to be tested than not.

246   *Patient-defined threshold for testing*

247   The patient-defined threshold for testing for *HLA-A*31:01*, based on the rate of severe ADRs was

248   10.20 per 10,000 patients (95% CI, 10.11 to 10.33) which exceeds the actual number of severe ADRs

249   identified through testing (7.28 per 10,000), suggesting that patients would accept a test.

250   *Scenario analysis*

251   Based on the characteristics of a test for *HLA-B*15:02* which, if implemented, is estimated to reduce

252   the risk of serious ADRs by 6.94 cases per 10,000 patients treated, the probability of patient uptake

253   is calculated as 61%. Total utility of testing was 0.32 compared with -0.13 for the untested cohort.

254   The patient-defined threshold for testing is 16.55 severe ADRs per 10,000, implying that testing for

255   *HLA-B*15:02* is also preferred, given that this value exceeds the true rate of serious ADRs of 9.70 per

256   10,000, if testing were implemented.

257   Two subgroups qualified for analysis, namely sex and age. Marginal rates of substitution indicated

258   that females were more willing than males to trade a reduction in the chance of remission for

259   reduction in the risk of the severe ADR. Females were willing to accept a 30.2 percentage point (95%

260   CI, 19.5 to 52.9) reduction in remission for a 0.1% reduction in the risk of severe ADR, compared with

                                                                                                          12

261   males who were only willing to exchange a 4.6 percentage point (95%CI, 0.7 to 11.2) reduction in

262   remission for the same 0.1% reduction in the risk of severe ADR. Differences in the rate of exchange

263   for remission and side-effects (MRS) were not statistically significant for age.

264   ***Physicians' DCE***

265   Eighty-three neurologists completed the questionnaire, the majority (n=69, 83%) were adult

266   neurologists. Sixty-four (80%) respondents self-rated their knowledge of pharmacogenetic testing as

267   'No / Superficial Awareness', with just 16 (20%) reporting 'Detailed Awareness'. Fifty-six (67%)

268   respondents had not requested any pharmacogenetic test in the previous year, while 21 had

269   requested tests on up to 5 occasions. Forty-three (52%) respondents had reviewed at least one

270   patient with a cutaneous ADR associated with carbamazepine in the previous year and 69 (83%)

271   respondents had initiated carbamazepine in at least one patient in the previous month.

272   Thirteen neurologists were non-traders, defined as respondents who always select A or B ('test' or

273   'no test') throughout the experiment, regardless of changes in the profiles. Ten neurologists selected

274   'no test' to all responses and 3 neurologists selected 'test' to all responses. As discussed in the

275   methods, pharmacogenetic testing is not currently mandatory and the decision whether to request a

276   test will depend on a number of professional factors and personal opinions. During the individual

277   interviews, a minority of neurologists were opposed to the introduction of pharmacogenetic testing

278   into routine clinical practice, even when presented with attributes demonstrating a clear clinical

279   benefit. In order to optimise our assessment of the attributes of a pharmacogenetic test valued by

280   neurologists, we excluded non-traders from the analysis presented. However, the statistically

281   significant attributes remained significant when non-traders were included in the model. The

282   coefficients of all attributes with the exception of time to test result were significant and in the

283   expected direction. Overall goodness of fit of the model was good. The odds that respondents

284   selected the test decreased by 1% for every £1 increase in the cost of testing. An increase of 1

285   percentage point in PPV increased the odds of preferring pharmacogenetic testing by 7%; reference

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286   to *HLA-A*31:01* testing in the BNF increased the odds that respondents would test by 58%; and a

287   test that predicts both severe and mild ADRs decreased the odds of testing by 31% (Table 4).

288   Marginal rates of substitution for the significant attributes indicated that neurologists were willing to

289   pay £5.87 for a 1 percentage point increase in NPV and £3.99 for an equivalent increase in PPV.

290   Respondents were willing to pay £31.29 for the coverage of mild in addition to severe cutaneous

291   ADRs, and £39.35 for the inclusion of testing advice in BNF (Table 4).

292   *Utility model*

293   The total utility of testing for *HLA-A*31:01* is positive at 6.36 (95% CI, 3.74 to 10.22), indicating a

294   general tendency to request the test (Table 5). Reducing the cost of testing from £100 to £35

295   increased the probability of requesting the test to 68.1%. A scenario in which the time to test result

296   is reduced from 4 to 2 days had little influence on the probability of requesting the test, but an

297   improvement in PPV from 26% to 70%, increased the probability of requesting the test almost 8-fold,

298   to 88.6%. An improved NPV of 99% compared to the existing 96% increased the probability of

299   requesting the test to 55.1%.

300   Insert Table 5 here

301   **Discussion**

302   Using a structured ranking exercise, we found that patients prioritised health outcomes relating to

303   the benefits of treatment, in terms of seizure freedom and associated adverse events. The results of

304   the DCE suggested that patients were willing to accept a less effective AED if that treatment had less

305   risk of harm. They were willing to forego a 1,760 per 100,000 chance of improvement in remission

306   for each 1 in 100,000 reduction in the risk of a severe ADR. When patient preferences were

307   analysed alongside data of actual event rates and characteristics of a test for *HLA-A*31:01*, the

308   results indicate that patients would prefer testing and being prescribed lamotrigine (conditional on

309   test result) to the current standard of care.   The current rate of ADR for patients who have the test

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310   is 7.28 per 10,000; if this were to increase by an additional 19 (or more) per 10,000, patients would

311   prefer standard care.

312   In contrast to patients, neurologists highlighted process-related outcomes. Their preference for

313   higher NPV might indicate a degree of caution in terms of wanting tests with a reduced likelihood of

314   false negative results that would require the prescribing of a second choice AED. They were willing

315   to pay an additional £58.67 per 10 percentage point increase in NPV. Neurologists were willing to

316   pay an additional £39.35 for a test which was included in the BNF. This attribute captures tests that

317   are recommended by regulatory agencies or included in clinical guidelines and are more likely to

318   have high PPV and NPV [22]. A pharmacogenetic test that was less expensive was predictably

319   preferred, but reduced turnaround time did not significantly influence the probability of requesting

320   the test.

321   The study benefitted from having taken a systematic and rigorous approach to identifying attributes

322   and levels that were both plausible and relevant to each perspective. For the DCE of patients, these

323   were derived from interviews, with the final selection of attributes and levels piloted in cognitive

324   interviews and presented in numerical and pictogram format to aid interpretation. A recent

325   systematic review found that DCE studies have been notoriously poor at reporting the methodology

326   supporting the explanation of risk and the validity of risk communication [23]. This study represents

327   a thorough application of cognitive interviews to support the face validity of the design of the DCE

328   and the presentation of risk attributes, and associated trading tasks. A comparable approach was

329   taken with neurologists, which included a literature review and structured interviews, consistent

330   with guidelines for DCE attribute selection [24].

331   Our inclusion of both patients' and clinicians' perspectives represents an important addition to the

332   emerging literature on preference-elicitation in pharmacogenetics. The finding that both groups

333   identified very different attributes but generally consistent preferences is reassuring in the context

334   of implementing a new health technology. Patients' acceptance of a decrease in treatment benefit

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335   for a reduced chance of serious adverse drug reactions – even if that chance is very small – implies

336   that patients will be satisfied with a prescription for a second choice AED which might not

337   necessarily be as effective as the first.

338   Payne et al. [13] evaluated patient and health care professionals' preferences, using DCE methods,

339   for pharmacogenetic testing of TPMT prior to treatment with azathioprine. Their study focused on

340   service delivery and found that patients valued accurate and timely information about the necessity

341   of the test and interpretation of the results. Our patient study differed as it focused on their

342   preference for different AEDs, accepting that the key consequence of a pharmacogenetic test is the

343   possibility of being prescribed an alternative medicine with a different safety profile, and potentially

344   reduced effectiveness. We subsequently modelled the scenario of pharmacogenetic testing using

345   additional information on the actual benefits of AEDs and test characteristics. This approach has the

346   advantage of acknowledging the broader clinical context of testing as opposed to the specific action

347   of whether or not to test. Importantly, we have derived the threshold at which patients' utility will

348   be maximised through testing prior to taking carbamazepine.

349   We are aware of two other DCEs of patients with epilepsy. Lloyd et al. [11] used a DCE to elicit the

350   importance of adverse events compared with seizure control for people with epilepsy and found

351   that patients preferred AEDs with less severe adverse events, greater control and least cost. This

352   direction of preferences was the same in our study, however, the amount of remission patients were

353   willing to forego for a 1% reduction in rash differed: 4.45% seizure control for 1% reduction in risk of

354   rash compared to a 0.58 percentage point reduction in remission for a 1 percentage point reduction

355   in rash in our study. This may be explained by differences in how attributes were presented in the

356   DCE, in our study we considered a 'potentially life threatening adverse drug reaction' that may

357   influence the strength of preference for other attributes. Lloyd et al. [11] also included cost,

358   whereas our study only focused on treatment benefits and harms.   More recently, Manjunath et al.

359   [12] included attributes for seizure frequency and, among others, 'short term' side effects

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360   (sleepiness, dizziness, headache, nausea, tremor, double or blurred vision, and skin rash) and 'long

361   term' side effects (fatigue, moodiness, confusion or memory problems). Patients with epilepsy

362   considered seizure reduction to be the top priority when ranked against the reduction or elimination

363   of side effects. However as with Lloyd et al. [11], there was no consideration of more serious ADRs

364   which respondents to our DCE considered important.

365   Our study had some limitations. The survey was conducted online which resulted in a self-selected

366   sample of patients. This may affect the generalizability of the findings, particularly given that access

367   to, and use of the internet will be variable among patients with epilepsy. Moreover, the sample

368   primarily represented prevalent cases with long-standing experience of epilepsy, compared to

369   incident cases who will be most commonly offered testing. In addition, the severity of epilepsy,

370   defined as the frequency of seizures, was not recorded in the survey. It is foreseeable that patients

371   with more severe epilepsy may be willing to trade a greater risk of ADR for an improvement in

372   seizure control. Nevertheless, the agreement of our findings with other such studies lends support

373   to the validity of the results. Common to all DCEs is the balance of comprehensiveness in the

374   selection of attributes included and ability of respondents to make rational choices. Our DCE of

375   patients was restricted to the 5 highest ranked attributes each with 2 levels, and only 5 patients did

376   not select the choice which was marginally dominant and this had no impact on the result. By

377   contrast, the DCE of physicians was somewhat more extensive with 6 attributes and 16 levels in

378   total, and 13 respondents were non-traders. Overall, however, we considered the impact of the DCE

379   designs not to have adversely affected the study conclusions. Finally, the study included a sample of

380   UK patients and neurologists and the characteristics of these groups as well as the nationally funded

381   healthcare system where patient care takes place, may limit the generalisability of results. In

382   particular, the extent to which the results of the assessment of neurologists' preferences for

383   pharmacogenetic testing can be extrapolated to other populations may be limited both by different

384   healthcare systems (for example privatised systems) and different ethnic populations where the risk

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385   of ADRs associated with carbamazepine may be different. However, importance of the significant

386   attributes of predictive accuracy (PPV, NPV) will likely translate across all populations.

387   In conclusion, our analysis of patient preferences indicates that patients value the reduction in risk

388   of severe ADR which could be achieved by pharmacogenetic testing prior to prescribing

389   carbamazepine. The DCE of neurologists would suggest that the most effective method of ensuring

390   that current pharmacogenetic tests are used more widely would be for the cost of testing to reduce.

391   Reassuringly, testing for *HLA-A*31:01* is cost-effective [25] meaning that turnaround time to result

392   will likely become important given there is often a clinical urgency and patient expectation for

393   treatment of uncontrolled seizures.

400   **Declaration:** The authors declare no conflict of interest and confirm to have read the Journal's

401   position on issues involved in ethical publication and affirm that this report is consistent with those

402   guidelines. All authors have completed the Unified Competing Interest form at

403   www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and

404   declare: no support from any organisation for the submitted work; no financial relationships with

405   any organisations that might have an interest in the submitted work in the previous 3 years; no

406   other relationships or activities that could appear to have influenced the submitted work.

407   **Contributions:** GP, EAFH, MP, AGM, DAH contributed substantially to the conception and design of

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409   EAFH, DAH drafted the paper and all authors revised it critically for important intellectual content,

410   and gave their final approval of the version to be published. All authors agree to be accountable for

411   all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of

412   the work are appropriately investigated and resolved.

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Figure 1: Example of binary choice DCE questions

Physician DCE	Patient DCE

Physician DCE

Question: "You have decided to prescribe carbamazepine for your patient. You may either select the following pharmacogenetic test prior to the prescription, or select not to test and proceed with the prescription blindly"

Cost	£35
Days to result	2
Positive predictive value (PPV)	2%
Negative predictive value (NPV)	70%
Coverage	Serious ADRs ONLY
Inclusion in British National Formulary (BNF)	Yes

☐ I WOULD select the test prior to the prescription of carbamazepine

☐ I WOULD NOT select the test and proceed with the prescription of carbamazepine blindly

Patient DCE

Question: "Which medication would you prefer?"

	MEDICATION A	MEDICATION B
Stop Seizures *One year after starting this medication*	5 in 10 people <u>seizures stop</u>	3 in 10 people <u>seizures stop</u>
Fewer Seizures *One year after starting this medication*	3 in 10 people <u>experience fewer seizures</u>	1 in 10 people <u>experience fewer seizures</u>
Mild skin rash *A blotchy, itchy red rash on your upper body*	1 in 100 people experience a mild skin rash	26 in 100 people experience a mild skin rash
Memory Problems *These are frequent and affect activities of daily life*	1 in 100 people experience memory problems	7 in 100 people experience memory problems
Potentially life-threatening reaction *Severe skin reaction that may cause death*	**UNCOMMON** More than 1 in 1000 people experience a life-threatening reaction	**RARE** More than 1 in 10,000 people experience a life-threatening reaction
Which medication would you prefer to take?	☐	☐

Table 1: Attributes and levels of the discrete choice experiments

Attribute	Description	Levels (code)	Rationale
Physicians' DCE			
Cost of Test	The total cost of the pharmacogenetic test in Pounds Sterling.	35 (0) 100 (1) 200 (2)	Cost attribute ranked highly by neurologists. Realistic levels based on expert opinion (M Pirmohamed).
Time to Result	The total time from initially requesting the pharmacogenetic test to receipt of result.	2 (0) 4 (1) 7 (2)	Time attribute ranked highly by neurologists. Realistic levels based on expert opinion (M Pirmohamed).
Positive Predictive Value (PPV)	The probability of experiencing the ADR if a positive result is identified on the pharmacogenetic test: the 'true positives'.	2 (0) 35 (1) 70 (2)	PPV attribute ranked highly by neurologists. Range of PPV values informed by literature review [5-7]
Negative Predictive Value (NPV)	The probability of not experiencing the ADR if a negative result is identified on the pharmacogenetic test: the 'true negatives'.	70 (0) 85 (1) 99 (2)	NPV attribute ranked highly by neurologists. Range of NPV values informed by literature review [5-7]
Coverage of Test	The ability of the pharmacogenetic test to predict severe ADRs only, or mild in addition to severe ADRs.	Severe Hypersensitivity Adverse Drug Reactions (0) Severe AND Mild Hypersensitivity Adverse Drug Reactions (1)	Parameter informed by the attributes of current alleles: *HLA-A*31:01* is associated with severe and mild ADRs [7], *HLA-B*15:02* is associated with severe ADRs only [5]
British National Formulary (BNF)	The inclusion or exclusion of the pharmacogenetic test in the drug information detailed under carbamazepine.	Test NOT INCLUDED in the BNF (0) Test INCLUDED in the BNF (1)	Regulatory approval and inclusion in clinical guidelines ranked highly by neurologists. Inclusion in the British National Formulary [16] was included in the DCE as a pragmatic marker of regulatory approval and clinical availability.
Patients' DCE			
Seizures Stop	The probability of patients achieving 1-year remission from seizures with AED	5 in 10 people (0.5) 3 in 10 people (0.3)	Primary outcome of AED studies is 12 month remission. Levels based on published clinical trial data [1].
Fewer seizures	The probability of patients experiencing	3 in 10 people (0.3)	Seizure reduction was the highest ranked outcome

		1 in 10 people (0.1)	by patients. Levels based on clinical trial data [1].
	fewer seizures after 1-year with AED		
Mild skin rash	The probability of patients experiencing a mild adverse drug reaction but which is sufficient to warrant change in AED	1 in 100 people (0.01) 26 in 100 people (0.26)	*HLA-A*31:01* allele is associated with mild hypersensitivity reaction with patients exposed to carbamazepine. Levels based on published data [1,7].
Memory problems	The probability of patients experiencing memory problems which are sufficient to warrant change in AED	1 in 100 people (0.01) 7 in 100 people (0.07)	Adults with established epilepsy and prescribing clinicians were most concerned about memory problems in ranking exercises. Levels based on published clinical trial data [1].
Potentially life-threatening reaction	The probability of patients experiencing a rare but severe skin reaction, described as hot, painful patches on the skin that can blister and risks death.	RARE: More than 1 in 10 000 people (0.0001) UNCOMMON: More than 1 in 1000 people (0.001)	*HLA-A*31:01* allele is associated with Drug Induced Hypersensitivity Syndrome (DIHS), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) with patients exposed to carbamazepine. Levels based on published data on allele associations [7] and SmPC for carbamazepine [17].

Table 2: Values of regression variables used to estimate utility, probability of test uptake and maximally tolerated rate of severe ADR for patients to prefer testing. Data are taken from source, or derived according to standard epidemiological calculations.

Attributes	Expected probabilities conditional on AED and *HLA-A*31:01* test result			Testing Strategy		Reference
	CBZ / -ve	CBZ / +ve	LTG / +ve	Test	No test	
Remission	36.000	36.000	29.000	35.8189	36.0000	[1]
Fewer seizures	17.370	17.370	21.430	17.4751	17.3700	[1]
Memory problems	3.1746	3.1746	2.6455	3.1609	3.1746	[1]
Skin rash	7.000	34.000	4.000	6.9224	7.6986	[1,7]
Severe ADR	0.0738	1.0895	0.0354	0.0728	0.1001	[7,15,17]

All data are reported as number of events per 100 patients.

Abbreviations: AED is anti-epileptic drug; CBZ is carbamazepine; LTG is lamotrigine; ADR is adverse drug reaction

Table 3: Patient characteristics

Patients' characteristics	n	%
Age: median (range)	38	(18-72)
Female	61	66.3
Time since diagnosis:		
Less than 4 months	1	1.1
4-12 months	3	3.3
1-5 years	14	15.4
6-10 years	12	13.2
More than 10 years	61	67.0
Seizure type:		
Focal	27	31.4
Complex focal	40	46.5
Absences, tonic, atonic	45	52.3
Tonic clonic	56	65.1
Time since last seizure:		
Less than a week	38	44.2
Less than a month	16	18.6
Less than 6 months	14	16.3
Less than a year	2	2.3
A year or over	16	18.6
Seizure frequency compared to 1 year ago:		
More often	19	22.1
Less often	26	30.2
About the same	41	47.7
Prescribed AED in past 3-months	85	98.8
Changes to AED in past 3-months:		
No change	54	63.5
Increased/decreased	25	29.4
Change of drug	9	10.6
Additional drug	12	14.1
Fewer drugs	2	2.4
Stopped altogether	1	1.2
Reason for changes:		
Lack of seizure control	30	90.9
Unpleasant side effects	14	42.4
Remission	1	3.0
Morisky non-adherence [21]	16	50.0
Experience of taking CBZ	31	36.5
Experience of adverse events:		
Change or stop due to memory problems	8	24.2
CBZ skin rash	10	18.5
CBZ severe ADR (requiring hospital treatment)	1	1.9
Living alone	13	15.9

In employment, education, or looking after home	49	60.5
Ethnicity:		
White	74	90.2
Black / African / Caribbean / Black British	3	3.7
Asian / Asian British	1	1.2
Mixed / Multiple ethnic groups	2	2.4

Table 4: Random effects logit regression model and marginal rates of substitution

DCE of patients			
Attribute	**Coefficient (95% CI)**	**Odds ratio**	**Remission (95% CI)**
Remission	0.037 (95% CI 0.032 to 0.054	1.04	1.00
Fewer seizures	0.011 (95% CI 0.003 to 0.024)	1.01	0.29 (95% CI 0.07 to 0.58)
Memory	-0.119 (95%CI -0.182 to -0.104)	0.89	-3.22 (95% -4.54 to -2.35)
Skin rash	-0.021 (95% CI -0.034 to -0.016)	0.98	-0.58 (95% CI -0.84 to -0.38)
Severe ADR	-6.490 (95% CI -10.295 to -5.467)	0.00	-175.83 (95% CI -253.30 to -121.42)
Constant	0.147 (95% CI -0.022 to 0.392)	1.16	

Pseudo-R^2 = 0.2118; Wald χ^2 140.34; Log likelihood = -382.74; p=0.00

DCE of neurologists			
Attribute	**Coefficient (95% CI)**	**Odds ratio**	**Willingness to pay (95% CI)**
Cost	-0.012 (95% CI -0.016 to -0.010)	0.99	- -
Time to Result	0.027 (95% CI -0.077 to 0.131)	1.03	- -
PPV	0.047 (95% CI 0.042 to 0.061)	1.05	3.99 (95% CI 3.00 to 5.37)
NPV	0.068 (95% CI 0.056 to 0.096)	1.07	5.87 (95% CI 4.04 to 8.46)
Coverage of Test	-0.365 (95% CI -0.774 to -0.095)	0.69	-31.29 (95% CI -60.06 to -7.20)
Included in BNF	0.459 (95% CI 0.140 to 0.865)	1.58	39.35 (95% CI 10.97 to 71.05)
Constant	-7.120 (95% -9.879 to -5.824)		

Pseudo-R^2 value 0.2294; Wald χ^2 199.74; Log likelihood = -529.66; p<0.001

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Table 5: Results of scenario analysis of varying attribute levels within plausible ranges on the total utility and probability of test uptake

Parameter	Attribute and levels	Utility	Probability of uptake
Base case	Cost: £100 Time to result: 4 Days PPV: 26% NPV: 96% Coverage of test: Severe and mild Included in BNF: No	6.3584 (95% CI: 3.7391 – 10.2210)	49.9%
Reduced cost	Cost: £35	7.117 (95% CI: 4.8012 – 10.8525)	68.1%
Reduced time to result	Time to result: 2 Days	6.3046 (95% CI: 3.8939 – 9.9629)	48.6%
Improved PPV	PPV: 70%	8.4055 (95% CI: 5.5658 – 12.8900)	88.6%
Improved NPV	NPV: 99%	6.5639 (95% CI: 3.9072 – 10.5111)	55.1%