Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Is pharmacogenetic testing effective for identifying risk of adverse drug reactions in people with epilepsy?

1. Purpose of the Evidence Appraisal Report

The Evidence Appraisal Report is a rapid systematic literature search of published evidence and websites to identify the best clinical and health economic evidence on health technologies. Researchers critically evaluate this evidence. The draft Evidence Appraisal Report is reviewed by experts and by Health Technology Wales (HTW) multidisciplinary advisory groups before publication.

2. Health problem

Epilepsy is a common neurological condition that affects approximately 0.5—1% of the population (Leach 2018). The initial choice of therapy for people newly diagnosed with epilepsy can depend on classification and whether the epilepsy is thought to be genetic, generalised or focal in onset. The National Institute for Health and Care Excellence (NICE) clinical guideline 137 (CG137) for epilepsy diagnosis and management includes guidance on first line anti-epileptic therapies; this guideline is being updated following a surveillance review in 2018 (NICE 2012). The majority of people with epilepsy (65—70%) will have attained seizure control with their first or second-line antiepileptic drug.

Although rare, some antiepileptic drugs can induce cutaneous adverse drug reactions (cADRs). Carbamazepine, for example, is associated with hypersensitivity reactions in up to 10% of patients, including severe conditions such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS) and hypersensitivity syndrome (HSS) (Yip&Pirmohamed 2017).

3. Health technology

Some adverse reactions to antiepileptic therapies have been associated with genetic markers; in particular, certain polymorphisms in human leukocyte antigen (HLA) alleles. Genetic testing for these genetic markers in newly diagnosed patients could identify people who are most at risk of adverse reactions and inform treatment choices.

The international Clinical Pharmacogenetics Implementation Consortium (CPIC) has issued several guidelines in relation to pharmacogenetics testing for epilepsy for particular antiepileptic treatments (Caudle et al. 2014, Phillips et al. 2018). Those relating to adverse reactions are described in Table 1 below.

Table 1. CPIC Guidelines for pharmacogenetics testing in people with epilepsy

Marker	Recommendation	Classification of recommendation	Guideline
HLA-B*15:02 negative and HLA-A*31:01 negative	Use carbamazepine per standard dosing guidelines.	Strong	Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update (Phillips et al. 2018).
HLA-B*15:02 negative and HLA-A*31:01 positive	If patient is carbamazepine-naive and alternative agents are available, do not use carbamazepine.	Strong	
	If patient is carbamazepine-naive and alternative agents are not available, consider the use of carbamazepine with increased frequency of clinical monitoring. Discontinue therapy at first evidence of a cADR.	Optional	
	The latency period for cADR is variable depending on phenotype; however, all usually occur within three months of regular dosing. Therefore, if the patient has previously used carbamazepine consistently for longer than three months without incidence of cADRs, cautiously consider use of carbamazepine.	Optional	
HLA-B*15:02 positive and any HLA-A*31:01 genotype (or HLA-A*31:01 genotype unknown)	If patient is carbamazepine naive, do not use carbamazepine.	Strong	
	The latency period for drug induced SJS/TEN is short with continuous dosing and adherence to therapy (4-28 days), and cases usually occur within three months of dosing; therefore, if the patient has previously used carbamazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine in the future.	Optional	
HLA-B*15:02 negative	Use oxcarbazepine per standard dosing guidelines.	Strong	
HLA-B*15:02 positive	If patient is oxcarbazepine-naive, do not use oxcarbazepine.	Strong	
HLA-B*15:02 positive	If patient is phenytoin naive, do not use phenytoin/ fosphenytoin.	Strong	Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing (Caudle et al. 2014).
cADR: cutaneous adverse drug reaction; SJS: Steven-Johnson syndrome; TEN: toxic epidermal necrolysis			

4. Evidence search methods

The Population-Intervention-Comparator-Outcomes (PICO) framework for the evidence appraisal (Appendix 1) was developed following comments from the HTW Assessment Group and UK experts. A systematic literature search was undertaken on 24 April 2019. The search strategy is available on request. This aimed to identify the following types of evidence:

(i) systematic reviews
(ii) health economic analyses
(iii) primary studies, and
(iv) ongoing clinical trials.

Background studies and other papers identified at the scoping stage were also assessed for relevance. Patient safety and organisational issues were identified from the papers included in the clinical effectiveness section and expert advice; no specific searches were undertaken.

5. Clinical effectiveness

5.1. Systematic review

No systematic reviews were identified that report pharmacogenetic testing in people with epilepsy to screen for susceptibility to adverse drug reactions.

5.2. Primary studies

Due to the lack of secondary evidence available, we identified primary studies investigating pharmacogenetic screening for susceptibility to adverse drug reactions in people with epilepsy. Two studies were identified that investigated pharmacogenetic screening prior to epilepsy treatment; specifically HLA genotyping prior to carbamazepine treatment (Mushiroda et al. 2018, Chen et al. 2011).

Mushiroda et al (2018) investigated use of HLA-A*31:01 screening prior to carbamazepine treatment; participants who were HLA-A*31:01 positive received an alternative drug to carbamazepine. Overall, there was a reduction in carbamazepine-induced adverse drug reactions in the study when compared to historical data from two different databank sources.

The second study investigated the use of HLA-B*15:02 screening prior to carbamazepine treatment (Chen et al. 2011); patients who were HLA-B*15:02 positive received an alternative drug to carbamazepine. Overall, there was a reduction in adverse reactions (SJS and TEN) compared to historical data.

Neither study population was specific to people with epilepsy, and instead included multiple conditions for which carbamazepine would be indicated. In the study screening for HLA-A*31:01, approximately 78% of study participants were people with epilepsy. In the study screening for HLA-B*15:02, 14.2% of participants were people with epilepsy.

Further study details and characteristics are described in Table 2 and Table 3.

5.3. Ongoing studies

We identified one ongoing trial: a prospective non-randomised multicentre study to assess the reductions of drug-induced adverse reactions following HLA screening (Second Affiliated Hospital of Guangzhou Medical et al. 2021). The study will include Han Chinese people that are going to receive an antiepileptic drug (including carbamazepine, oxcarbazepine, lamotrigine, phenobarbital and phenytoin) as a new therapy. HLA screening will be used prior to initiating therapy to guide the choice of treatment. The primary outcome measure is the incidence of anti-

epileptic drug-induced cADRs within the first three months of commencing therapy. The estimated study completion date is June 2021.

The topic proposer (manufacturer MC Diagnostics) noted that there are plans for two pilot studies planned in Wales that will investigate use of pharmacogenetics in Wales using multi-gene panel testing, which will include HLA-testing for carbamazepine[1]. They also reported a planned multi-gene panel pilot in England that features HLA.

[1] Maguire P. et al; MC Diagnostics. Personal communication, 22 October 2019.

Table 2. Mushiroda, et al. (2018)

Descriptive details	PICO	Quality of study	Observations/notes
Multicentre (n= 36), Japan. Baseline characteristics: **Negative for HLA-A*31:01 (n = 932) / Positive for HLA-A*31:01 (n = 198)** Male: 510 (54.7%) / 104 (52.5%) Age, mean (range), years: 37.1 (0 to 95) / 38.5 (0 to 89) Indicated for carbamazepine based on epilepsy: 737 (78.5%) / 151 (75.9%) Other indications for carbamazepine included schizophrenia, bipolar disorder, trigeminal neuralgia, or other. Recruitment period: January 2012 to November 2014.	**Population:** (1) those deemed suitable to start treatment with carbamazepine based on the decision of neuropsychiatrists at cooperating hospitals (2) those of Japanese descent of any age who had not received carbamazepine within 1 month of enrolment, and (3) those patients (or guardians) providing written informed consent. Exclusion criteria: history of carbamazepine-induced cADRs, pregnancy (or planned pregnancy), and/or renal failure. **Intervention:** Rapid genotyping method to detect HLA-A*31:01 using a DNA chip (ROKEN Genesis) prior to treatment (Aoki et al. 2012). **Comparator:** historical controls from: (1) BioBank Japan clinical database (searched April 2003 to December 2010). (2) Japan Medical Data Centre (JMDC) claims database (searched January 2005 to December 2014) **Outcomes:** Incidence of carbamazepine-induced cADRs.	**Study design:** Blood samples were obtained from each participant in the intervention arm and screened for HLA-A*31:01. The HLA status was reported to the neuropsychiatrists within 1.5 hours, who then explained the results and risk of carbamazepine-induced cADRs to the participant or guardian. Patients who were negative for HLA-A*31:01 received carbamazepine; those who were positive for HLA-A*31:01 were prescribed alternative drugs according to neuropsychiatrist recommendation. Telephone interviews with participants were conducted once weekly for 8 weeks to monitor for symptoms of cADRs or discontinuation of drugs.	• The intervention was validated using additional samples from each participant, using WAKFlow HLA typing kit (Wakunaga), based on a Luminex system. The study reports no difference between the two assays. • The study included people who were indicated for carbamazepine for other conditions, such as schizophrenia. This is also likely the case for the historical control group. • Participants were not limited to those with newly diagnosed epilepsy, and may have received previous carbamazepine treatment. The proportion of participants who are newly diagnosed is not clear. • The authors report that 8 weeks follow-up was chosen as most carbamazepine-induced cADRs occur within 2 months of treatment initiation. • One patient who tested positive for HLA-A*31:01 was assigned carbamazepine by choice of the neuropsychiatrist; they did not develop cADRs.

Results	Authors' observations

Incidence of carbamazepine-induced cADRs

Adverse event	Genetic screening group (n = 1,130)	Historical controls	
		BioBank Japan data (n = 1,312)	JMDC claims database (n = 12,060)
All carbamazepine-induced cADRs, n (%)	23 (2.0)*	44 (3.4)	610 (5.1)
SJS or TEN	0	3	6
Drug-induced hypersensitivity syndrome	3	1	N/A
Maculopapular eruption	9	6	N/A
Erythema multiforme	5	15	N/A
Fixed drug eruption	0	0	N/A
Others	0	8	N/A
Unknown	6	11	N/A
Odds ratio (95% CI) for incidence of any carbamazepine-induced cADR		0.60 (0.36-1.0)	0.39 (0.26-0.59)
p-value		0.048	<0.001
*All 23 patients who developed definite or probable carbamazepine-induced cADRs were negative for HLA-A*31:01			

Discontinuations

	HLA-A*31:01 positive (n = 198)	HLA-A*31:01 negative (n = 932)	p-value
Discontinuation due to cADRs, n (%)	4 (2.0)	43 (4.6)	0.12
Carbamazepine-induced			
Definite	0	11	
Probable	0	12	
Possible	1	9	
Unlikely	3	11	

Comparison with a historical control indicated that the pre-emptive use of HLA-A*31:01 genetic screening in the present study was associated with a 40% reduction in the incidence of carbamazepine-induced cADRs. The frequency of HLA-A*31:01 carriers in the population was high (17.7%) in this study, although previous reports have also indicated a similar expected frequency of HLA-A*31:01 carriers (16.6%-17.5%). These results suggested that HLA-A*31:01 genetic screening would be useful for the prevention of carbamazepine-induced cADRs among Japanese patients.

For carbamazepine-induced cADRs, the clinical utility of the HLA-B*15:02 genetic test has already been established by pre-emptive screening, and the test is recommended in the Clinical Pharmacogenetics Implementation Consortium guidelines. However, the frequency of the HLA-B*15:02 allele is low in Korean, Japanese, African, and European populations. In addition, HLA-B*15:02 is specifically associated with SJS/TEN. By contrast, HLA-A*31:01 is associated with carbamazepine-induced cADRs in Japanese, Han Chinese, Northern European, Korean, and Canadian populations… Moreover, HLA-A*31:01 has been associated with a full spectrum of carbamazepine-induced cADRs. Therefore, HLA-A*31:01 genetic screening prior to prescribing carbamazepine would be useful for preventing many types of carbamazepine-induced cADRs in a range of patient populations.

Our study showed that HLA-A*31:01 screening was associated with a significant reduction in the incidence of carbamazepine-induced cADRs; however, a 2.0% incidence of carbamazepine-induced cADRs still remained. This indicates that even patients who tested negative for HLA-A*31:01 should be monitored for cADRs.

CI: confidence interval; cADR: cutaneous adverse drug reaction; SJS: Steven-Johnson syndrome; TEN: toxic epidermal necrolysis

Table 3. Chen, et al. (2011)

Descriptive details

Multicentre (n= 23), Taiwan.

Baseline characteristics

	Negative for HLA-B*15:02 (n = 4,483)	Positive for HLA-B*15:02 (n = 372)	Total (n = 4855)
Male, n (%)	2132 (47.6)	193 (51.9)	2325 (47.9)
Age, mean (range), years	56.5 (0.6 to 98.2)	55.7 (4.3 to 91.4)	56.5 (0.6 to 98.2)
Indicated for carbamazepine due to epilepsy, n (%)	632 (14.1%)	57 (15.3)	689 (14.2)

Other conditions indicated for carbamazepine included neuralgia, diabetes-related neuropathic pain, tinnitus, bipolar or other psychiatric disorder, or other.

Recruitment period: July 2007 to April 2010

PICO

Population: people between the ages of six months and 99 years who had not previously received carbamazepine and who would have normally received carbamazepine at the time of the study.

Exclusion criteria: history of carbamazepine allergy, bone marrow transplantation, non-Han Chinese descent

Intervention: Real-time PCR-based genotyping for HLA-B*15:02

Comparator: historical controls: cases taken from the NHIRD database, 2002 to 2004, where carbamazepine was prescribed for at least 14 days, were used to estimate incidence of carbamazepine-induced SJS/TEN.

Outcomes: Incidence of SJS/TEN, adverse events.

Quality of study

Study design: Patients attended an initial screening clinic; all patients were prescribed carbamazepine at this time but asked to refrain from taking it until the genetic results had been obtained. Blood samples were obtained and sent for HLA-B*15:02 genotyping. The results were reported to physicians within two to three days.

At this time patients negative for HLA-B*15:02 started carbamazepine treatment, while positive patients attended a second clinic visit and were recommended alternative drugs.

Once weekly telephone interviews were performed with all patients for the following 8 weeks to monitor for adverse drug reactions.

Observations/notes

- To validate the real time PCR assay, the first 2,000 samples were tested using a HLA sequence-specific oligonucleotide reverse line blot. All tested samples were consistent.
- The study included people who were indicated for carbamazepine for conditions other than epilepsy. This is also likely for the historical data.
- The authors reported that two-month follow-up would be sufficient to observe incidence of carbamazepine-induced SJS/TEN.

Results

Incidence of carbamazepine-induced cADRs

Adverse event	Current study	Historical controls		
		2002	2003	2004
New recipients of carbamazepine, n	4,120	50,971	48,522	49,670
Subjects with ICD-9-CM diagnostic code 695.1†, n	-	1,441	1,261	1,354
Carbamazepine-induced SJS/TEN, n	0	123	108	116
Incidence of carbamazepine-induced SJS/TEN, %	0	0.24	0.22	0.23
p-value*, comparison between the historical incidence and incidence in current study		<0.001	<0.001	<0.001
†ICD code for erythema multiforme including hypersensitivity reactions				

Authors' observations

"Our findings suggest that screening patients for the HLA-B*15:02 allele before the initiation of carbamazepine treatment and withholding carbamazepine treatment from HLA-B*15:02-positive patients can reduce the incidence of carbamazepine-induced SJS/TEN among Han Chinese.

It is possible that some of the drug-related adverse reactions we observed were early SJS lesions or that early withdrawal of carbamazepine may have prevented a more severe SJS–TEN or TEN-like reaction. However, we think that this is unlikely, since once patients are sensitized by carbamazepine and have early blisters or ulcers, SJS–TEN progresses, even after the withdrawal of the drug. SJS–TEN did not develop in any of the subjects who completed the two-month follow-up.

*p-value was calculated using fishers' exact test

Adverse events during the 2-month follow-up

Adverse event	HLA-B*15:02 positive with alternative medication (n = 215)	HLA-B*15:02 negative with carbamazepine (n = 4,120)	Total
Mild cutaneous events			
Rash and itching	5*	206	211
Rash, itching and blisters	1**	20	21
Rash, itching and oral ulcers	0	14	14
Rash, itching, blisters and oral ulcers	0	7	7
Itching, blisters and oral ulcers	0	2	2
Blisters and oral ulcers	0	3	3
Severe cutaneous events			
Maculopapular eruption	0	3	3
Hypersensitivity syndrome	0	2	2
Urticaria	1***	1	2
SJS/TEN	0	0	0
Other adverse events****			
Fever	1	92	93
Sore throat	4	126	130
Fatigue	16	818	834
Dizziness	10	497	507
Insomnia	5	197	202
GI symptoms	4	185	189

*Among these 5 subjects, the alternative drugs were gabapentin, lamotrigine, naproxen, imipramine, and prednisolone.
**This subject had rash, itching and blisters after taking gabapentin. Symptoms were mild and disappeared after seven days.
***This subject had taken oxcarbazepine before study enrolment
****Subjects may have had more than one adverse event. Adverse events with low frequency are not listed.

Our results suggest the value of HLA-B*15:02 screening to prevent carbamazepine-induced SJS/TEN. However, as for any new pharmacogenetic test, it is important to document the use and safety of alternative medications."

CI: confidence interval; cADR: cutaneous adverse drug reaction; SJS: Steven-Johnson syndrome; TEN: toxic epidermal necrolysis; ICD: International Classification of Diseases

6. Economic evaluation

6.1. Health economic literature review

The titles and abstracts of 2,992 records identified in the search for this research question were screened and 10 health economic studies were deemed potentially relevant. The full texts of these studies were reviewed against the inclusion/exclusion criteria. Following consideration of the full texts, nine studies were excluded from the review. Two studies were excluded as they are not economic evaluations (Arnaout et al. 2013, Powell et al. 2015), one study describes a methodology for assessing the cost effectiveness of multi-gene panel testing (Plumpton et al. 2018), and six studies are based in non-OECD countries (Chen et al. 2016, Chong et al. 2017, Dong et al. 2012, Dong et al. 2013, Rattanavipapong et al. 2013, Tiamkao et al. 2013). One published health economic study with the relevant comparison was included in this review (Plumpton et al. 2015) and is summarised in Table 4 below.

The study used a Markov model to assess the cost effectiveness of using HLA-A*31:01 testing to determine whether carbamazepine should be prescribed. The analysis assumes that carbamazepine is prescribed if the test result is negative and lamotrigine is prescribed if the test result is positive. This strategy was compared against carbamazepine prescribing without HLA-A*31:01 testing. In both strategies, it was assumed that patients that experienced a cADR would be switched to treatment with valproate.

The results of the analysis showed that the HLA-A*31:01 testing strategy was more effective (0.0234 QALYs) and more costly (£300.39). The resulting ICER of £12,808 per QALY is below the NICE threshold of £20,000 per QALY suggesting that the HLA-A*31:01 testing strategy is cost-effective.

Deterministic sensitivity analysis showed that that treatment efficacy, utilities and drug costs were the main drivers of the cost effectiveness result. Probabilistic sensitivity analysis showed that HLA-A*31:01 testing had an 80% probability of being cost-effective at a threshold of £20,000 per QALY.

The study was assessed as being directly applicable as it considered the UK NHS perspective. It was also considered to be of generally high quality but had several potential limitations, such as a possible underestimation of adverse drug reactions in the arm prescribed carbamazepine.

Table 4. Included Study: Plumpton et al (2015)

Study details	Study population and design	Data sources	Results	Quality assessment
Author and year: Plumpton et al 2015 **Country:** United Kingdom **Type of economic analysis:** Cost utility analysis **Perspective:** UK NHS **Currency:** UK pound sterling (£) **Price year:** 2010/2011 **Time horizon:** Lifetime **Discounting:** Costs and benefits discounted at 3.5% per year **Source of funding:** The research is supported by the NIHR Cochrane	**Population characteristics** Carbamazepine-naïve people with focal-onset seizures who were newly diagnosed or had failed treatment with previous monotherapy or had relapsed from a period of remission following withdrawal of treatment. A hypothetical cohort of 38 year old males with 12 seizures per year were modelled in the analysis. **Modelling approach** Model consisted of a decision tree and Markov model. The decision tree was used to capture the first three months of treatment. Markov state transition model was used to model longer term consequences over the patient's lifetime. Markov model included health states for remission, uncontrolled seizures and death. This Markov structure was replicated for each of the possible antiepileptic drugs included (carbamazepine, lamotrigine and valproate). A cycle length of one year was used. **Treatment strategies** **Intervention**: Testing for *HLA-A*31:01* allele and prescribing carbamazepine if negative or lamotrigine if positive **Comparator**:	**Source of baseline and effectiveness data:** Pharmacogenetic data were sourced from published study on association. Prevalence of HLA-A*31:01, adverse drug reaction probabilities and mortality were sourced from published literature. Effectiveness of treatments for partial epilepsy were sourced from SANAD RCT and a multiple treatment comparison of treatments for epilepsy. Annual probabilities of treatment failure and remission were sourced from NICE CG137 Epilepsies: diagnosis and management (2012) **Source of resource use and cost data:** Costs of carbamazepine, lamotrigine and valproate were sourced from SANAD RCT data, which was recorded at three months and one year and then annually for duration of RCT. ME resource use was estimated based on assumption from CG137. HSS and SJS/TEN resource use was based on systematic review of case management studies, of which 30 HSS cases and 12 SJS/TEN cases were included. As in SANAD trial: drugs, hospitalisations, investigations, appointments with health care professionals. Genotyping, including initial screen and second high-resolution test in those who test positive.	**Base case analysis** **Total costs:** With test: £10,808 Without test: £10,508 *Incremental:* £300.39 (95% CI: £133.60 to £343.92) **Effectiveness**: With test: 15.7744 QALYs Without test: 15.7510 QALYs *Incremental:* 0.0234 QALYs (95% CI: NR) **ICER:** £12,808 per QALY gained **Deterministic sensitivity analysis:** One-way sensitivity analysis showed that efficacies utilities and costs of drugs were the main drivers of cost effectiveness. When these inputs for lamotrigine were set equal to the corresponding values for valproate, testing was dominated. Structural sensitivity analysis showed that results are not sensitive to changing the assumption of a constant remission rate after year 3. **Probabilistic sensitivity analysis:** Probabilistic sensitivity analysis showed that testing for *HLA-*	**Applicability** Analysis is directly applicable as it considers the UK NHS perspective. **Limitations** The analysis was generally considered to be of high quality but some potential limitations were noted. • Modelling approach has led to a lower probability of cADRs in people taking carbamazepine than reported in the SANAD trial. • Uncertainty around QoL values used for disutilites because they are based on approximations from other conditions. • Cost and QoL consequences of ME may have been overestimated as they were estimated separately to the SANAD RCT which reported that there was no significant difference between those who did and did not experience ME. • Assumes valproate would be used if treatment with carbamazepine or lamotrigine was ineffective but alternative treatments are more likely to be used in current practice • Model assumed a constant rate of seizures with no possibility for seizure reduction.

Study details	Study population and design	Data sources	Results	Quality assessment
Programme Grant Scheme **Potential conflict of interest:** None	Prescription of carbamazepine without *HLA-A*31:01* testing In both arms, patients are assumed to be switched to valproate following a cADR. Valproate is not associated with ME or HSS and the probability of SJS/TEN is assumed negligible in the model.	NHS unit costs 2010/2011 were sourced from Finance department of Royal Liverpool and Broadgreen University Hospital Trust and PSSRU. Cost of genotyping was based on estimates from NHS Blood and Transplant Service **Source of health related quality of life (QoL) data:** Health state QoL values were estimated using EQ-5D data (using UK tariff). Carbamazepine, lamotrigine and valproate utilities were obtained from SANAD RCT. One year data was used for decision tree and two year data was used for Markov model. Disutilites associated with cADR were estimated based on approximations from similar health states in the literature: Atopic dermatitis was used for ME; Sepsis was used for HSS; Severe burns was used for SJS/TEN. For long term SJS/TEN utility, patient-level data for people surviving TEN obtained from literature (SF-36 mapped to EQ-5D).	*A*31:01* allele had an 80% probability of being cost-effective at a threshold of £20,000 per QALY.	• There is no possibility for antiepileptic dose adjustment in the model • Markov state transitions were not permitted from remission to uncontrolled epilepsy.

Additional notes

The analysis is principally concerned with the use of testing to guide treatment choice to reduce cADRs. However, it should be noted that the effectiveness of the medications in terms of their efficacy in treating epilepsy is a key driver of the results. Indeed, the positive cost-effectiveness result associated with testing is driven to a large extent by the higher clinical effectiveness of lamotrigine compared with carbamazepine. This raises the possibility that treating everyone with lamotrigine (without testing) may be the most cost-effective strategy. However, this treatment strategy was not considered in the analysis.

Utility and cost data were adjusted using linear regression for age, gender, number of seizures in previous year, antiepileptic drug and trial arm as a proxy for epilepsy type.

cADR: cutaneous adverse drug reaction; CI: confidence interval; CUA: cost-utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health]); HSS: hypersensitivtiy syndrome; ICER: Incremental Cost-Effectiveness Ratio; ME: maculopapular rash; NR: not reported; pa: probabilistic sensitivity analysis; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life-year; QoL: quality of life; RCT: Randomised Controlled Trial; SF-36: 36-item Short Form Survey; SJS/TEN: Steven-Johnson syndrome/toxic epidermal necrolysis.

7. Organisational issues

One study was identified that investigated patient and physician preferences for pharmacogenetics testing prior to carbamazepine treatment (Powell et al. 2015). The physician discrete choice experiment (DCE) was completed by 83 neurologists. The majority of respondents (77%) reported "no/superficial awareness" of pharmacogenetics testing, and 67% had not requested pharmacogenetics testing within the last year. Cost, inclusion on the British National Formulary, coverage, negative predictive value and positive predictive value were all considered significant attributes. The neurologists were willing to pay £5.87 for a 1% increase in negative predictive value and £3.99 for a 1% increase in positive predictive value. Overall, the study demonstrated limited awareness or use of pharmacogenetics testing

HTW sought expert opinion to establish current practice for newly-diagnosied epilepsy treatment in Wales. We were advised that other anti-epileptic drugs, such as levetiracetam or lamotrigine, are preferred over carbamazepine[2]. This is supported by a study observing trends in prescription of anti-epileptic drugs in Wales between 2000 and 2010 (Pickrell et al. 2014). The study showed a significant decrease in the proportion of carbamazepine and phenytoin prescriptions, compared to a significant increase in the proportion of lamotrigine and levetiracetam prescriptions. Welsh prescribing data provided by the Wales Analytical Prescribing Unit (WAPSU) shows that, from January-December 2018, carbamazepine was prescribed for epilepsy in 9.5% of cases in primary care.

The topic proposer MC Diagnostics reported that their multi-gene panel test would require minimal training and set-up[3]. It was also noted that, as part of the Welsh pilots discussed in Section 5.3 Ongoing studies, MC Diagnostics is prepared to install instrumentation and train users at no additional cost (based on a minimum study cohort of 3,000 tests).

8. Patient issues

Powell et al. (2015) performed a DCE on 92 people with epilepsy in the UK, four of whom has been diagnosed within the last year. The majority of patients were taking anti-epileptic drugs (n = 85). Over a third (n = 31) had received carbamazepine, and one patient had experienced a severe carbamazepine-induced skin reaction that resulted in hospitalisation. Another 10 patients had experienced carbamazepine skin reactions.

Overall, patients were willing to accept a reduction in the chance of seizure remission for a reduction in adverse events. Estimated utility associated with testing for HLA-A*31:01 was greater, at 0.52 (95% CI 0.19, 1.00) than not testing at 0.33 (95% CI −0.07, 0.81). This resulted in an estimation of 55% test uptake by patients.

Scenario analysis explored screening with HLA-B*15:02. The probability of uptake was 61%, and clinical utility of testing was 0.32 compared to −0.13 for not testing.

It is worth noting that as the majority of patients were not newly diagnosed or naïve to carbamazepine treatment, preferences may be affected by these experiences. The reported study characteristics did not include ethnicity, a factor which may have impact on patient preferences due to the known increased risk of carbamazepine induced reactions in people of Asian descent.

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[2] Smith P.; Consultant neurologist, Cardiff and Vale University health board. Personal communication, DATE. Pickrell W. O.; Consultant neurologist, Swansea Bay University health board. Personal communication, 28 October 2019.

[3] Maguire P. et al; MC Diagnostics. Personal communication, 22 October 2019.

9. Conclusions

The purpose of this report was to identify evidence on the effectiveness of pharmacogenetic testing for people with newly diagnosed epilepsy prior to epilepsy treatment as a method of identifying people with a high risk of adverse drug reactions.

This report identified two studies that use HLA genotyping to inform carbamazepine treatment: the first used HLA-A*31:01 testing in the Japanese population, and the second used HLA-B*15:02 testing in the Taiwan population. Both studies demonstrated a reduction in adverse reactions in the total study population compared to historical data. However, both studies included patients who were indicated for carbamazepine for conditions other than epilepsy. It is uncertain what impact this would have on the applicability of the results to people with epilepsy. Furthermore, the studies were conducted in countries that will have different HLA allele frequencies compared to the UK.

One relevant cost-effectiveness study was identified which considered the use of HLA-A*31:01 testing to determine whether carbamazepine should be prescribed. This study was directly applicable to the NHS setting, but had several limitations.

The results of the analysis suggest that the HLA-A*31:01 testing strategy is cost-effective in comparison to carbamazepine prescribing without testing. Uncertainty analysis suggested that the result was reasonably robust with an 80% probability of HLA-A*31:01 testing being cost-effective at £20,000 per QALY in probabilistic sensitivity analysis. However, while the study was directly applicable to the NHS setting and generally thought to be of high quality, it did have some potential limitations which should be taken into consideration. Furthermore, expert opinion suggests that carbamazepine is no longer given as first line treatment with patients instead given a drug with a much lower rate of ADRs. As such, the applicability of the analysis to current practice is somewhat diminished.

In conclusion, the evidence to inform the use of pharmacogenetics testing to avoid adverse drug reactions in people with epilepsy is currently very limited. The two studies identified in this report included populations outside of people with epilepsy and in populations where the HLA allele frequencies may be higher.

10. Further research

Large studies investigating the use of pharmacogenetic screening to guide treatment for newly diagnoses epilepsy are recommended. This includes tests for HLA alleles, as well as other potential candidates that have been identified as having an association with drug-induced adverse reactions.

11. Contributors

This topic was proposed by MC Diagnostics.

The HTW staff and contract researchers involved in writing this report were:

- L Elston – reviewed clinical and cost-effectiveness evidence and lead author of report
- S Hughes – reviewed cost-effectiveness evidence and authored the economic evaluation section of report
- M Prettyjohns – quality assurance of report
- J Washington – developed search strategy and carried out literature searches

The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

12. References

Aoki M, Hosono N, Takata S, et al. (2012). New pharmacogenetic test for detecting an HLA-A 31: 01 allele using the InvaderPlus assay. Pharmacogenetics and Genomics. 22(6): 441-6. doi: https://dx.doi.org/10.1097/FPC.0b013e3283527c40

Arnaout R, Buck TP, Roulette P, et al. (2013). Predicting the cost and pace of pharmacogenomic advances: An evidence-based study. Clinical Chemistry. 59(4): 649-57. doi: http://dx.doi.org/10.1373/clinchem.2012.199455

Caudle KE, Rettie AE, Whirl-Carrillo M, et al. (2014). Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. Clinical Pharmacology & Therapeutics. 96(5): 542-8. doi: https://dx.doi.org/10.1038/clpt.2014.159

Chen P, Lin JJ, Lu CS, et al. (2011). Carbamazepine-induced toxic effects and HLA-B 1502 screening in Taiwan. New England Journal of Medicine. 364(12): 1126-33. doi: https://dx.doi.org/10.1056/NEJMoa1009717

Chen Z, Liew D, Kwan P. (2016). Real-world cost-effectiveness of pharmacogenetic screening for epilepsy treatment. Neurology. 86(12): 1086-94. doi: https://dx.doi.org/10.1212/WNL.0000000000002484

Chong HY, Mohamed Z, Tan LL, et al. (2017). Is universal HLA-B 15:02 screening a cost-effective option in an ethnically diverse population? A case study of Malaysia. British Journal of Dermatology. 177(4): 1102-12. doi: https://dx.doi.org/10.1111/bjd.15498

Dong D, Sung C, Finkelstein A. (2013). Cost-effectiveness of HLA-B[*]1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore. Neurology. 80(17): 1621-2. doi: http://dx.doi.org/10.1212/WNL.0b013e3182915be2

Dong D, Sung C, Finkelstein EA. (2012). Cost-effectiveness of HLA-B 1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore. Neurology. 79(12): 1259-67. doi: https://dx.doi.org/10.1212/WNL.0b013e31826aac73

Leach JP. (2018). Treatment of epilepsy - Towards precision [version 1; referees: 3 approved]. F1000Research. 7 (no pagination)(1932). doi: http://dx.doi.org/10.12688/f1000research.16448.1

Mushiroda T, Takahashi Y, Onuma T, et al. (2018). Association of HLA-A 31:01 Screening With the Incidence of Carbamazepine-Induced Cutaneous Adverse Reactions in a Japanese Population. JAMA Neurology. 75(7): 842-9. doi: https://dx.doi.org/10.1001/jamaneurol.2018.0278

NICE. (2012). Epilepsies: diagnosis and management. Clinical guideline (CG137). National Institute for Health and Care Excellence.

Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. (2018). Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. Clinical Pharmacology & Therapeutics. 103(4): 574-81. doi: https://dx.doi.org/10.1002/cpt.1004

Pickrell WO, Lacey AS, Thomas RH, et al. (2014). Trends in the first antiepileptic drug prescribed for epilepsy between 2000 and 2010. Seizure. 23(1): 77-80. doi: https://doi.org/10.1016/j.seizure.2013.09.007

Plumpton CO, Pirmohamed M, Hughes DA. (2018). Cost-Effectiveness of Panel Tests for Multiple Pharmacogenes Associated With Adverse Drug Reactions: An Evaluation Framework. Clinical Pharmacology & Therapeutics. 22: 22. doi: https://dx.doi.org/10.1002/cpt.1312

Plumpton CO, Yip VL, Alfirevic A, et al. (2015). Cost-effectiveness of screening for HLA-A 31:01 prior to initiation of carbamazepine in epilepsy. Epilepsia. 56(4): 556-63.

Powell G, Holmes EA, Plumpton CO, et al. (2015). Pharmacogenetic testing prior to carbamazepine treatment of epilepsy: patients' and physicians' preferences for testing and service delivery. British Journal of Clinical Pharmacology. 80(5): 1149-59. doi: https://dx.doi.org/10.1111/bcp.12715

Rattanavipapong W, Koopitakkajorn T, Praditsitthikorn N, et al. (2013). Economic evaluation of HLA-B 15:02 screening for carbamazepine-induced severe adverse drug reactions in Thailand. Epilepsia. 54(9): 1628-38. doi: https://dx.doi.org/10.1111/epi.12325

Second Affiliated Hospital of Guangzhou Medical U, Guangzhou First People's H, West China H, et al. (2021). HLA Screening in Reducing the Risk of Antiepileptic Drug-induced Cutaneous Adverse Reactions.

Tiamkao S, Jitpimolmard J, Sawanyawisuth K, et al. (2013). Cost minimization of HLA-B 1502 screening before prescribing carbamazepine in Thailand. International Journal of Clinical Pharmacy. 35(4): 608-12. doi: https://dx.doi.org/10.1007/s11096-013-9777-9

Yip VL, Pirmohamed M. (2017). The HLA-A 31:01 allele: influence on carbamazepine treatment. Pharmacogenomics & Personalized Medicine. 10: 29-38. doi: https://dx.doi.org/10.2147/PGPM.S108598

Appendix 1. PICO framework

Research Question	In people with newly diagnosed epilepsy, is pharmacogentic testing effective for detecting and reducing the risk of adverse reactions to anti-epileptic medications?

P (population)	People with newly diagnosed epilepsy or unprovoked isolated seizures in whom management with first-line anti-epileptic drugs is indicated.
I (intervention)	Genetic testing to screen for alleles (including, but not limited to HLA-B*15:02 or HLA-A*31:01) indicating susceptibility to adverse reactions to anti-epileptic medications (including, but not limited to carbamazepine, oxcarbazine, lamotrigine, levetiracetam or phenytoin)
C (comparator(s))	No susceptibility testing prior to prescribing, or any non-genetic method of susceptibility testing prior to prescribing.
O (outcomes)	Detection rate of adverse drug reaction susceptibility Reduction in adverse drug reactions Rate of adverse drug reactions (mild, severe) Mortality Health related quality of life Changes in patient management

Appendix 2 - PRISMA flow diagram outlining selection of papers for clinical and cost effectiveness