Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Inform discussions on new topics received by HTW.
2. Determine the quantity and type of evidence available on a topic.
3. Assess the topic against HTW selection criteria.

Topic:	Pharmacogenetic tests to identify risk of adverse reactions to anti-epileptic medications
Topic exploration report number:	TER017
Referrer:	MC Diagnostics
Topic exploration undertaken by:	Health Technology Wales

Aim of Search

Health Technology Wales researchers searched for evidence on the effectiveness of pharmacogenetic testing for detecting and reducing the risk of adverse reactions to anti-epileptic medications in people with newly diagnosed epilepsy.

Summary of Findings

Guidelines

No individual guidelines were identified on the subject of genetic testing and adverse drug reactions. However, Swen et al (2011) is an update of guidelines by the Royal Dutch Association for the Advancement of Pharmacy giving pharmacogenetics-based dosing recommendations for 53 drugs.

Systematic Reviews of Clinical Evidence

No systematic reviews were identified that considered the effectiveness of multi-gene panel testing in people with newly diagnosed epilepsy, or the associated alleles.

Sychev & Malova (2015) is a general systematic review of pharmacogenetics and concludes that 'clinical use of pharmacogenetic testing seems to be most appropriate for the management of patients with high risk of adverse drug reactions'. Phillips et al (2001) conducted a general systematic review on the potential role of pharmacogenomics in reducing the incidence of adverse drug reactions. The review included 11 adverse drug reaction studies and 22 review articles describing variant alleles of drug-metabolising enzymes.

Systematic Reviews of Economic Analyses

Two systematic reviews of economic analyses of pharmacogenomics tests that aim to reduce the incidence of adverse drug reactions were identified. These included the Beaulieu et al (2010) and Plumpton et al (2016) studies. The systematic review of pharmacoeconomic studies by Beaulieu et al included 15 studies, but found a high degree of heterogeneity even between those studies which evaluated the same pharmacogenomics tests. The populations considered by the studies were unclear. The systematic review of economic evaluations by Plumpton et al included 47 studies considering pharmacogenetic testing in a range of populations. Evidence indicated that testing for HLA-B*15:02 and HLA-A*31:01 (alleles associated with risk of adverse event resulting from treatment with carbamazepine) is cost effective.

Other Economic Analyses

Alagoz et al (2016) demonstrated that one-time genetic testing is cost effective in the United States, with an incremental cost effectiveness ratio of $53,680 per QALY gained. The test and population considered in the base case is not clear.

Four studies investigated carbamazepine and HLA-B*15:02 or HLA-A*31:01: Dong et al (2012), Plumpton et al (2015), Tiamkao et al (2013) and Hung and Chung (2013). All four show that genetic testing for their allele of interest was cost effective for some or all of the population. Only the Plumpton study used a UK perspective, concluding that 'testing for HLA-A*31:01 in order to reduce the incidence of cutaneous adverse drug reactions in patients being prescribed carbamazepine for epilepsy is likely to represent a cost-effective use of health care resources'.

Conclusions

A substantial body of evidence, including systematic reviews and economic evaluations, exists on the use of pharmacogenetic testing to assess and manage the risk of adverse drug reactions. However, the systematic reviews identified do not specifically focus on pharmacogenetics testing in newly-diagnosed epilepsy. Economic analyses were identified in the relevant population and in the UK setting: this evidence predominantly considers carbamazepine and further assessment would be needed to establish the level of evidence that exists for other drugs of relevance.

Areas of Uncertainty

The exact list of anti-epileptic medications that may cause hypersensitivity reactions, and therefore where pharmacogenetics tests may have value, needs to be refined: this will be done as part of the developing the appraisal scope.

Feasibility of Technology Assessment

HTW's Assessment Group concluded to progress this topic to Evidence Appraisal. This will be published as EAR010.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland:	We did not identify any relevant guidance from this organisation.
Health Technology Assessment Group	We did not identify any relevant guidance from this organisation.
Health Information and Quality Authority	We did not identify any relevant guidance from this organisation.
UK guidelines and guidance	
SIGN	We did not identify any relevant guidance from this organisation.
NICE	We did not identify any relevant guidance from this organisation. Several NICE Guideline make recommendations on the use of genetic testing, but not in the context of pharmacogenetics/susceptibility to adverse drug reactions.
Secondary literature and economic evaluations	
Cochrane library	We did not identify any Cochrane Reviews on genetic testing and adverse drug reactions.
Medline	*Systematic Reviews:* 1. Swen, J. J., et al. (2011). "Pharmacogenetics: from bench to byte--an update of guidelines." Clinical Pharmacology & Therapeutics **89**(5): 662-673. 2. Sychev, D. A. and E. U. Malova (2015). "Evidence-based pharmacogenetics: Is it possible?" International Journal of Risk & Safety in Medicine **27 Suppl 1**: S97-98. 3. Phillips, K. A., et al. (2001). "Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review." JAMA **286**(18): 2270-2279 Twenty-one other systematic reviews were identified that did not mention any drug or allele relevant to the population of interest, but discussed genetic testing and adverse drug reactions. Diseases included: HIV/AIDS, gout, cardiovascular disease, leprosy, breast cancer (other alleles), depression, tuberculosis and lung cancer, while the drugs were abacavir, allopurinol, dapsone, warfarin, thiopurine, tramadol, psychotropics and anaesthetics. *Economic Analyses:* 1. Alagoz, O., et al. (2016). "Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions." Pharmacogenomics Journal **16**(2): 129-136. 2. Beaulieu, M., et al. (2010). "Systematic review of pharmacoeconomic studies of pharmacogenomic tests." Pharmacogenomics **11**(11): 1573-1590. 3. Dong, D., et al. (2012). "Cost-effectiveness of HLA-B 1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore." Neurology **79**(12): 1259-1267. 4. Plumpton, C. O., et al. (2016). "A Systematic Review of Economic Evaluations of Pharmacogenetic Testing for Prevention of Adverse Drug Reactions." Pharmacoeconomics **34**(8): 771-793.

	5. Plumpton, C. O., et al. (2015). "Cost-effectiveness of screening for HLA-A 31:01 prior to initiation of carbamazepine in epilepsy." Epilepsia **56**(4): 556-563.. 6. Tiamkao, S., et al. (2013). "Cost minimization of HLA-B 1502 screening before prescribing carbamazepine in Thailand." International Journal of Clinical Pharmacy **35**(4): 608-612. Nineteen other studies were identified which did not consider the population of interest (relevant drugs or alleles), but discussed the economics of pharmacogenetic testing in different populations.
Primary studies	
Medline	We did not search specifically for primary studies; those listed are below are relevant primary studies that were retrieved in secondary studies searches. • Chung, W. H., et al. (2014). "Genetic variants associated with phenytoin-related severe cutaneous adverse reactions." JAMA 312(5): 525-534. • Nguyen, D. V., et al. (2016). "Validation of a novel real-time PCR assay for detection of HLA-B 15:02 allele for prevention of carbamazepine - Induced Stevens-Johnson syndrome/Toxic Epidermal Necrolysis in individuals of Asian ancestry." Human Immunology **77**(12): 1140-1146.
Ongoing trials	
Clinicaltrials.gov	We did not identify any relevant ongoing trials.
Ongoing secondary research	
PROSPERO database	• Ana Alfirevic, Munir Pirmohamed, Branka Marinovic, Andrea Jorgensen, Linda Harcourt-Smith. Genetic testing for prevention of severe drug-induced skin rash [Cochrane Protocol]. PROSPERO 2015 CRD42015016870 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42015016870

Date of search:	Initial searches where carried out in October 2018, and refined/updated in December 2018.
Concepts used:	multi-gene panel tests, genetic testing and adverse drug reactions