

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1769 – Human leukocyte antigen (HLA) testing for hypersensitivity to carbamazepine and oxcarbazepine

Applicant: The Royal College of Pathologists of Australasia

Date of MSAC consideration: 3-4 April 2025

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of human leukocyte antigen *HLA-A*31:01* and *HLA-B*15:02* genotyping to predict carbamazepine- (CBZ) or oxcarbazepine-related (OXC) drug hypersensitivity reactions in patients who are about to commence carbamazepine or oxcarbazepine treatment was received from the Royal College of Pathologists of Australasia (RCPA) by the Department of Health and Aged Care.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of a new Medicare Benefits Schedule (MBS) item for human leukocyte antigen (HLA)-A*31:01 and HLA-B*15:02 genotyping to predict the risk of carbamazepine- (CBZ-) or oxcarbazepine- (OXC-) related drug hypersensitivity reactions in patients who are about to start or during the initiation of CBZ or OXC treatment. MSAC considered that there was a high clinical need for this testing because such hypersensitivity reactions although rare can be severe and life-threatening, and this testing was already recommended in clinical guidelines. MSAC noted that although the test identifies patients who have a higher risk for developing hypersensitivity reactions, the absence of these variants does not definitively rule out the risk of such reactions occurring. MSAC considered patients who tested variant-positive would generally use a different medicine. MSAC considered that this would be unlikely to lead to harm as there were multiple effective alternative treatments available.

MSAC considered that the testing was cost-effective based on the cost per patient with identified positive genotyping results, and the costs to the MBS were modest. MSAC supported a fee of \$139. MSAC advised that the MBS item should reflect a preference that testing occurs prior to treatment initiation, except in cases of clinical urgency when treatment needs to be started immediately prior to the availability of test results. MSAC also recommended that the MBS item should state that testing is 'at least' for two HLA variants without specifying the variants to allow testing of other relevant variants in the future. MSAC considered the MBS item should contain an explanatory note outlining testing should include at least HLA-A*31:01 and HLA-B*15:02, that a negative test does not exclude the possibility of a drug hypersensitivity reaction, and the recommendation for testing to occur prior to commencement of treatment. MSAC advised the listing should be reviewed after two years.

MSAC confirmed the following MBS item descriptor and explanatory note:

Table 1

Category 6 – PATHOLOGY SERVICES	Group P7 – Genetics
MBS item AAAA Genetic testing for at least two HLA variants to predict risk of carbamazepine- or oxcarbazepine-related severe drug hypersensitivity reactions in a patient, where the service is conducted prior to or during the initiation of treatment with carbamazepine or oxcarbazepine. Once per lifetime Fee: \$139.00, 75% = \$104.25, 85% = \$118.15	
Explanatory note: P.N.X.XX – Genetic testing for HLA variants to predict risk of carbamazepine- or oxcarbazepine-related severe drug hypersensitivity reactions – Item AAAA Genetic testing: • should be in line with contemporaneous guidelines published by clinical organisations such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) or The Epilepsy Society of Australia. • should at a minimum include the following alleles: <i>HLA-B*15:02</i>, <i>HLA-A*31:01</i> • should be preferably conducted prior to initiation of treatment with carbamazepine or oxcarbazepine, unless the patient requires urgent treatment before the test result is available. Requesting physicians should note: • Not all drug hypersensitivity reactions to carbamazepine or oxcarbazepine are linked to <i>HLA-B*15:02</i>, <i>HLA-A*31:01</i>. Thus, genetic testing cannot definitively exclude the possibility of a drug hypersensitivity event. Clinical vigilance remains necessary, even after negative results from the relevant HLA alleles testing. • <i>HLA-B*15:02</i> is of higher prevalence in patients with East Asian ancestry.	

Consumer summary
This is an application from the Royal College of Pathologists of Australasia requesting Medicare Benefits Schedule (MBS) listing of genetic testing of human leukocyte antigen (<i>HLA</i>) variants to determine the risk of hypersensitivity to carbamazepine (CBZ) and oxcarbazepine (OXC). <i>HLA</i> genes are genes that determine the ability of a body's immune system to distinguish between that body's own cells and the cells of foreign invaders like viruses and bacteria. <i>HLA</i> variants are different forms of a <i>HLA</i> gene which are naturally occurring. CBZ and OXC are medicines that are used to treat epilepsy and some other conditions. Some people can have serious, life-threatening reactions to these medicines. These serious reactions are more common in people who have one or more specific types of <i>HLA</i> variants. Having one of these <i>HLA</i> genes does not <i>guarantee</i> a person will have a serious reaction, however. Sometimes, people who don't have the <i>HLA</i> genes can still have serious reactions . This application is for testing of a person's <i>HLA</i> variants before they start treatment with CBZ or OXC. If the person is positive for one or more of the <i>HLA</i> variants associated with serious reactions to CBZ or OXC, they can choose to have a different medicine to avoid the risk of the reactions. MSAC considered that the <i>HLA</i> test was safe and accurate in detecting the <i>HLA</i> variants. MSAC considered that the test should be used as a way for clinicians and patients to assess a patient's risk of having a serious reaction, not as a definite diagnosis of a sensitivity to the

Consumer summary

medicines. MSAC also considered that there might be some uncommon cases where treatment needs to start urgently before the test results are known. MSAC considered that this was acceptable and should be up to the clinician and the patient to decide their risks and benefits.

MSAC considered that the proposed fee for the test was too high and advised the department to revise this. MSAC considered the test was good value for money, and the overall cost of the test to the MBS was modest.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported MBS listing of genetic testing of *HLA* variants for hypersensitivity to CBZ and OXC. MSAC considered the test to be safe and accurate, that it would help avoid serious harm for some patients, and that it was likely good value for money.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted the purpose of this application was to request MBS funding for testing of *HLA*-A*31:01 and *HLA*-B*15:02 variants to predict carbamazepine (CBZ) and oxcarbazepine (OXC)-related drug hypersensitivity reactions in patients about to start these treatments.

MSAC noted that CBZ and OXC are often used first line for the treatment of epilepsy (mainly focal) and trigeminal neuralgia. In addition to common side effects, several severe, painful, life-threatening reactions can occur in some people, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and eosinophilia and systemic symptoms syndrome (DRESS). These reactions are more common people with *HLA*-A*31:01 or *HLA*-B*15:02 variants (including many people with Asian ancestry), but not exclusively. Positive status for these variants generally correlates with a risk of hypersensitivity reactions insofar as people with one or more of these variants are more prone to hypersensitivity reactions, but the likelihood of a reaction actually occurring is variable and not definitive. Similarly people without these variants cannot be definitively ruled out from having a hypersensitivity reaction. MSAC therefore considered *HLA* testing to be a risk prediction tool rather than a diagnostic tool. A positive result after testing would likely lead to avoidance of CBZ or OXC to avoid the risk of severe adverse reactions, and treatment with an alternative drug. MSAC considered that there was a clinical need for this test given that hypersensitivity reactions although rare can have severe health consequences for patients and given that this test is currently recommended in clinical guidelines, albeit the Australian Therapeutic Guidelines advises testing for people of Asian ancestry. MSAC noted feedback from the applicant's pre-MSAC response that *HLA* genotyping in general has been broadly adopted and testing for the *HLA*-B*15:02 variant specifically remains a frequently requested test.

MSAC reviewed the clinical management algorithm. MSAC supported the Department's proposal that the item descriptor should state that testing is conducted prior to or during initiation of treatment. MSAC considered that, ideally and routinely, tests should be ordered and test results known before starting treatment with CBZ or OXC. However, MSAC noted that, particularly for patients with trigeminal neuralgia who often experience severe pain, there may be an urgent need to start treatment as soon as possible and it may not be appropriate to wait to start treatment before test results are known. In these exceptional and urgent cases, MSAC considered that it was acceptable to start treatment before the outcome of the test is known. MSAC advised that these considerations including the preference for testing prior to initiation of treatment should be included in the explanatory note to the MBS item descriptor and the decision on when to test should be driven by clinical judgement.

MSAC reviewed the proposed MBS item descriptor and confirmed that it should be agnostic to the medical condition requiring treatment with CBZ or OXC and specify that it test for a minimum

of two variants, while the Explanatory Note should specify that such testing should include both *HLA-A*31:01* and *HLA-B*15:02* variants. MSAC considered that it was critical to explain in the Explanatory Note that not all drug hypersensitivity reactions to carbamazepine or oxcarbazepine are linked to the variants of interest and genetic testing cannot definitively exclude the possibility of a drug hypersensitivity event. MSAC noted that the pre-MSAC response had proposed a slightly amended version of the Explanatory Note that involved referring the patient to genetic counselling but MSAC preferred the Explanatory Note as proposed by the Department (Table 1). MSAC also supported the Explanatory Note including text recommending that genetic testing should be in line with contemporaneous guidelines published by clinical organisations such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) or The Epilepsy Society of Australia.

MSAC considered that the indication for the test should not be expanded to include all drugs of the dibenzazepine class noting that the applicant's pre-MSAC response and consultation feedback from the Australian and New Zealand Association of Neurologists also did not support such expansion. MSAC noted that, if the test was performed once per lifetime, the test result would need to be available to all treating clinicians throughout the patient's life. MSAC noted the proposed fee of \$188 and considered that this fee was too high and this was not adequately justified. MSAC noted that the applicant's pre-MSAC response did not support the Department's proposal to reduce the fee to \$139 on the basis that it may restrict testing to only the highest-volume laboratories, limit access, and increase turnaround times. However MSAC agreed with the Department's proposed revised fee of \$139 because it aligned with *HLA-B27* assay pricing and because pathology providers performing the proposed service are also eligible for an additional MBS rebate payable under patient episode initiations. MSAC considered it would be informative for the department to develop a schedule of fees for genetic tests according to test methodology and use, to help the committee provide consistent advice on appropriate costs for genetic tests.

Regarding comparative safety, MSAC considered the analytical performance of the test to be robust although the diagnostic yield was dependent on ancestry and considered the clinical claim of noninferior safety of the test to be appropriate. Any change in management following a positive test result would likely also be non-inferior, as there are several alternative drugs available on the Pharmaceutical Benefits Scheme (PBS) as noted from the consultation feedback from the Australian and New Zealand Association of Neurologists. MSAC also noted that the applicant's pre-MSAC response identified a 2022 Cochrane review which showed that alternative antiepileptic drugs have non-inferior safety and effectiveness compared to CBZ and OXC.¹ However the applicant was unable to identify any Cochrane reviews comparing the relative effectiveness of OXC or CBZ with relevant comparators for other indications such as bipolar disorder or trigeminal neuralgia.

Regarding comparative clinical effectiveness, MSAC noted the lack of direct comparative evidence for tests for both alleles being performed together, the lack of evidence linking the test to health outcomes of overall morbidity and mortality, and the lack of data for the Australian population (particularly for First Nations people). MSAC noted that the pre-MSAC response acknowledged that much of the international evidence came from studies conducted in Asian populations but argued that this remains highly relevant to Australia's mixed ethnic population and highlighted that although self-identification of ethnicity can be inaccurate, as of the 2021 census, 17.4% of the Australian population identified as having wholly or partial Asian ancestry, meaning that the available evidence was applicable to a large subset of the Australian population.

MSAC agreed with ESC that there is evidence for clinical effectiveness if testing for each variant is assessed separately; however, diagnostic yield and prognostic accuracy are highly variable and

¹ Nevitt SJ, Sudell M, Cividini S, Marson AG, Tudur Smith C. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. *Cochrane Database of Systematic Reviews*. 2022(4).

dependent on population ancestry and the type of adverse reaction avoided, with linked evidence of superior effectiveness of testing in some populations. MSAC noted the evidence that implementation of policies for HLA-B*15:02 genotyping prior to the commencement of CBZ in East Asian populations reduces CBZ prescribing and reduces incidence of severe cutaneous adverse reactions (SCARs). However, MSAC agreed with ESC that this evidence is retrospective and specific to those populations and was therefore at high risk of bias. MSAC noted that HLA-B15:02 testing is currently recommended in Australian Therapeutic Guidelines before starting CBZ therapy, but that this advice is only listed as a footnote to the main guidance.

MSAC discussed the economic evaluation, which was a cost-effectiveness analysis (cost per patient per severe adverse reaction avoided) and cost-utility analysis (one for epilepsy and one for trigeminal neuralgia) with a stepped decision tree and Markov model. MSAC agreed with ESC that the economic model contained major flaws, leading to highly uncertain outputs. This included many questionable assumptions due to the scarcity of clinical evidence and in particular direct evidence on the tests for both variants being used together which flowed over into questionable outcomes in the modelling. MSAC noted that the economic model had been significantly revised following ESC advice to eliminate errors, including changing the model structure from assessing the probability of adverse events based on HLA variant status to assessing the probability of changing treatment. MSAC noted that late feedback received from the Australia and New Zealand Association of Neurologists suggested that levetiracetam, rather than sodium valproate, should have been used as the alternative medication in the model for epilepsy. However, MSAC noted that this would likely not have a large effect on the economic model, but may have a financial impact on PBS costs.

MSAC noted that the incremental quality-adjusted life year (QALY) gains were very small, but considered that this was to be expected given that changes in quality of life due to use of treatment with and without the test only occurred in a short period of time relative to the lifetime time horizon used in the model. MSAC therefore considered that the cost utility analysis model was unlikely to capture the true effect of adverse events and was therefore unhelpful for decision making. MSAC noted that the incremental cost-effectiveness ratio (ICER) was highly volatile in response to changes in inputs and model assumptions – the original model showed that the cost per QALY gained following HLA genotyping for epilepsy was dominant, but the revised model resulted in an ICER of \$825,763. For the cost per pain-controlled case of trigeminal neuralgia, the original model resulted in a cost of \$712.06, but was dominated by usual care in the revised model. This volatility was also reflected in the sensitivity analyses which showed that multiple drivers have a large impact on the model. For instance, MSAC noted that reducing the probability of patients treated with CBZ or OXC who transitioned from uncontrolled epilepsy to remission from the base case of 0.702 to 0.561 (i.e. by 20%) brought the ICER down to \$51,359 while increasing this base case probability to 0.842 (i.e. by 20%) resulted in a dominated ICER. Similarly reducing the annual cost of remission treated by CBC/OXC without SJS-TEN/DRESS by 20% increased the ICER to more than \$1.6 million while reducing it by 20% reduced the ICER to \$15,981. MSAC noted that the pre-MSAC response identified a cost-effectiveness analysis of HLA-B*15:02 genotyping albeit only focusing on Asian Australian patients which estimated an ICER of \$15,839 per QALY.²

Given these uncertainties, MSAC considered that the results of the stepped cost effectiveness analysis showing a cost of \$3337 per patient identified with positive genotyping results was a more reliable indicator of cost effectiveness. MSAC considered this was consistent with its previous assessments of genetic tests. However overall MSAC noted that the interpretation of the economic evaluation results should be approached with caution because of the insufficient evidence to determine the effectiveness of testing in reducing morbidity and mortality, the evidence regarding variant frequencies across different population groups was not robust, no

² Gu Y, Shih STF, Geevasinga N, Chan L, Frew JW, Sebaratnam DF. Economic Evaluation of HLA-B*15:02 Genotyping for Asian Australian Patients With Epilepsy. JAMA Dermatol. 2024;160(6):631-40.

Australian studies or data was available to inform the key modelling assumptions and the costing of hypersensitivity reactions was not accurate.

MSAC noted the financial and budgetary analysis and considered that the financial impact to the MBS was modest, although uncertain. Using a test fee of \$139, the cost ranged from \$541,747 in year 1 to \$789,767 in year 6, based on an uptake of about approximately 9,500 patients per year, which would decrease after year 1. MSAC agreed with ESC that the expected uptake of testing was unclear and highly uncertain.

Overall, MSAC supported the creation of a new MBS item for the proposed testing because of the high clinical need for this testing so that the targeted population can avoid rare but severe and life-threatening hypersensitivity reactions. In addition, MSAC considered that this testing is already recommended in clinical guidelines and given that the analytical performance of the genotyping method is robust, the cost per patient with identified positive genotyping results were within range of other MSAC supported genotyping germline tests and the financial implications to the MBS were low.

MSAC noted that there were also value of knowing benefits from testing insofar as it may provide greater certainty during decision-making. MSAC noted that HLA genotyping does not have the same ethical considerations as other types of genetic testing as the test only provides useful information for an individual about their risk of experiencing hypersensitivity reactions.

MSAC advised that education for providers on the availability of these tests on the MBS was critical to ensure provider awareness and avoidance of serious adverse events following treatment, and to mitigate the risk of litigation if a test is available but not used.

MSAC noted there were remaining concerns with equity and access, particularly for people living in rural and remote regions, including First Nations people, because testing is not yet widely available, meaning that test specimens may need to be sent interregional or interstate which may further delay treatment commencement. MSAC also noted the current lack of evidence for test outcomes in First Nations people. MSAC noted the pre-MSAC response acknowledged that known barriers to testing in First Nations communities are not easily overcome nor are they unique to this application, but asserted that this is more reason to support MBS funding of this testing. MSAC noted the pre-MSAC response considered that the testing is amenable to buccal swabs/saliva samples, which will ensure the test is more accessible.

MSAC noted and agreed to ESC's advice that building an ancestry registry for research in the Australian population could guide population analysis and future testing. MSAC recommended that the MBS listing be reviewed after 2 years and that such a review should consider both the testing uptake and its impact on the PBS.

4. Background

MSAC has not previously considered *HLA-A*31:01* and *HLA-B*15:02* genotyping to predict carbamazepine- or oxcarbazepine-related drug hypersensitivity reactions in patients who are about to commence carbamazepine or oxcarbazepine treatment.

5. Prerequisites to implementation of any funding advice

There are no prerequisites to be met.

6. Proposal for public funding

The intervention proposed is human leukocyte antigen (*HLA*) genotyping targeting at least two *HLA* gene variants before the commencement of carbamazepine- or oxcarbazepine (to identify

patients at risk of severe drug hypersensitivity reactions). The proposal intends to create a new MBS item (Table 2).

Table 2 Proposed item descriptor for HLA genotyping

Category 6 – PATHOLOGY SERVICES	Group P7 – Genetics
MBS item AAAA Genetic testing for <i>HLA</i> variants to predict risk of carbamazepine- or oxcarbazepine-related severe drug hypersensitivity reactions in a patient, where the service is conducted prior to the initiation of treatment with carbamazepine or oxcarbazepine. Once per lifetime	
Fee: \$188 Benefit: 75%=\$141.00 85%=\$159.80	
Note: Genetic testing to be conducted in line with current guidelines and should include at least (but not limited to) <i>HLA-B*15:02</i> and <i>HLA-A*31:01</i> .	

Source: p24 of the of the [ratified PICO](#)

Abbreviations: HLA = human leukocyte antigen

PASC considered that additional relevant *HLA* alleles may be discovered in the future and enter clinical guidelines, and that specifying the *HLA* alleles to be genotyped within the MBS item descriptor as proposed was insufficient to futureproof the item. PASC advised that the alleles to be genotyped should be moved from the item descriptor to an explanatory note, to allow this testing to be more easily updated in the future if needed. PASC also considered that the explanatory note should specify “at least” *HLA-B*15:02* and *HLA-A*31:01*, to further clarify the expectation that this testing also encompass any other alleles that are identified in the future as needing to be included in this testing.

PASC accepted the applicant’s advice regarding the DCAR base case which should use the applicant’s proposed fee (\$188) and explore the impact of the fee on the cost-effectiveness and cost as per usual. There was no justification provided for the proposed fee. The proposed fee is the same as the proposed fee in similar application MSAC 1760, which is also for pre-treatment genotyping, and lodged by the same applicant. However, there are some differences between the two applications mainly in the number of variants being analysed.

The proposed fee is much higher than MBS item 73320 (\$40.55) for detection of *HLA-B27* by nucleic acid amplification, MBS item 73317 (\$36.45) for detecting genetic mutations for haemochromatosis and MBS item 71151 (\$118.85) for phenotyping or genotyping of 2 or more antigens of or *HLA-DR*, *HLA-DP* and *HLA-DQ*. There are no commercial tests available for the proposed genetic variant combination, but Sonic Genetics lists a test for *HLA-B*15:02* at \$80.

7. Population

There was one PICO set provided, defining the population as all patients who are about to commence a treatment protocol that includes CBZ or OXC. The intervention was described as *HLA* genotyping to predict drug related hypersensitivity reactions to CBZ or OXC therapy in patients with epilepsy, trigeminal neuralgia or bipolar disorder. The intervention would be carried out in addition to CBZ or OXC therapy and take place before the commencement of either therapy.

8. Comparator

The comparator is no pre-treatment *HLA-A*31:01 and HLA-B*15:02* genotyping.

Currently (in the absence of *HLA* genotyping) all patients receive standard-dose CBZ or OXC and changes to therapy are made only if clinical signs of drug hypersensitivity reactions develop.

PASC agreed the comparator was no pre-treatment genotyping.

9. Summary of public consultation input

Consultation input was received from one individual consumer, one individual health professional, and six organisations. The organisations that provided input were:

- Australasian College of Dermatologists (ACD)
- Australian Pathology
- Epilepsy Society of Australia (ESA)
- Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT)
- The Royal Australian & New Zealand College of Psychiatrists (RANZCP)
- The Society of Hospital Pharmacists (SHPA)

Level of support for public funding

All organisations and individuals were supportive of public funding.

Comments on PICO

- The feedback advocated not to limit the indication to epilepsy and trigeminal neuralgia and to expand indications to include all patients about to commence treatment with carbamazepine to identify individuals at high risk of toxicity.
- The feedback also suggested not to limit the test to one ancestry and highlighted the risk of ethnicity assumptions due to diverse ancestry of the Australian population.
- The feedback noted significant use of carbamazepine in the neurodiverse population, with established evidence for use in paediatric patients.

Perceived Advantages

Advantages of the service noted in the input included:

- Prevent the occurrence of severe cutaneous reactions including hospitalisations, and reduce morbidity and mortality.
- Reduction of associated costs as a result of a serious adverse reaction.
- Improved safety with identification of individuals at increased risk of hypersensitivity reactions and allowing clinicians to consider suitable alternative medicines.
- Remove financial barriers for patients to access testing.

Perceived Disadvantages

Disadvantages of the service noted in the input included:

- Challenges for variant interpretation - *HLA-A*31:01 and HLA-B*15:02* genotyping can only provide information on the genes and regions included in the tests. Pharmacogenes are highly polymorphic because they may have undergone very minimal or no selection against variation.
- Potential short delays in treatment commencement while waiting for the results of the test.

- Patients may be referred for genetic counselling if the patient has concerns about familial implications, even though this type of pharmacogenetic testing has no inherited disease related implications.

Support for Implementation /issues

- In regards to the proposed service fee, the feedback highlighted two related MBS items with lower service fees for extensive HLA testing. These were item 71149 (\$108.25) for full HLA-A and HLA-B typing and item 71151 (\$118.85) for full HLA class 2 HLA-DR, HLA-DP and HLA-DQ typing. Feedback considered \$188 as a more realistic current cost of providing this testing. The feedback queried whether a new item number is needed and stated that testing provided in item 71149 would give the results needed to determine risk of carbamazepine sensitivity.
- The feedback agreed the proposed service descriptor supported an item that could include additional known HLA risk variants, however with respect to test “prior to initiation of treatment”, Australian Pathology indicated the difficulties for pathology providers to verify the treatment status before test. ASCEPT feedback queried if the item descriptor stating ‘specialist or consultant physician’ captured all relevant prescribers such as anaesthetists, pain specialists and psychiatrists.
- The consumer described their experience with the lack of testing prior to initiation of prescribed medications and having to tolerate severe adverse events requiring hospitalisation which could have been avoided with prior testing.

10. Characteristics of the evidence base

There was no direct evidence to assess the proposed intervention (*HLA-A*31:01* and *HLA-B*15:02* genotyping) prior to the commencement of CBZ or OXC) with the comparator (no pre-treatment genotyping). There was, however, direct evidence to assess *HLA-B*15:02* genotyping alone prior to the commencement of CBZ only, which was presented to support linked evidence for the intervention (combined *HLA-A*31:01* and *HLA-B*15:02* genotyping).

A summary of the key features of the studies providing direct from test to health outcome evidence is provided in Table 3.

Table 3 Key features of the included evidence comparing HLA testing for hypersensitivity to CBZ and OXC.

Trial/Study	Study design Risk of bias	Population	Intervention Adherence to intervention	Comparator	Key outcome(s)	Results used in economic model?
Chang et al. 2023 Taiwan	Retrospective longitudinal study High risk of bias	N = 45,348,457 episodes Where an “episode” is classified as a patient having ≥2 outpatient visits or ≥1 hospitalisation due to epilepsy or neuralgia (any type) within a calendar quarter.*	Reimbursed <i>HLA-B*15:02</i> genotyping before prescribing CBZ Information on policy adherence NR	Non-reimbursed <i>HLA-B*15:02</i> genotyping before prescribing CBZ (pre-reimbursement)	- Change in management (CBZ and OXC use) - Incidence of SCARs (total) - Incidence of SJS-TEN	Not used, as this was for genotyping for <i>HLA-B*15:02</i> alone and the study focused on the Taiwan population.
Chen et al. 2014 Hong Kong	Retrospective longitudinal study High risk of bias	N = 111,242 patients	Implemented policy of <i>HLA-B*15:02</i> genotyping before prescribing CBZ Practice was adherent to policy in 26.4% of patients, nonadherent in 19.0%, indeterminate in 54.6%.^	No policy of <i>HLA-B*15:02</i> genotyping before prescribing CBZ (pre-policy)	- Change in management (CBZ and OXC use) - Incidence of SJS-TEN	Not used, as this was for genotyping for <i>HLA-B*15:02</i> alone and the study focused on the Hong Kong population.

Abbreviations: CBZ=carbamazepine; OXC=oxcarbazepine; SCAR=severe cutaneous allergic reactions; SJS-TEN=Stevens-Johnson syndrome/Toxic epidermal necrolysis

*The same patient could appear in different quarters, because they may have many episodes of epilepsy or neuralgia over time.

^“Adherent” practice was defined as CBZ commencement within 6 months of a negative test or commencement of a non-CBZ AED within 6 months of a positive test. “Nonadherent” practice was defined as CBZ commencement without confirmation of *HLA-B*15:02*-negative status, either when there was no testing completed or when CBZ was commenced before the test result was available. “Indeterminate” practice was any which could not definitively be classified as either adherent or nonadherent.

11. Comparative safety

There was no direct evidence for safety related to *HLA-A*31:01* and *HLA-B*15:02* genotyping. Adverse events of the test itself are expected to be minimal given that genotyping is minimally invasive, with samples using common DNA testing methods (via blood test, cheek swab). Psychological harms are unlikely given that *HLA-A*31:01* and *HLA-B*15:02* only have clinical relevance for predicting hypersensitivity in the use of specific drugs such as CBZ and OXC. Therefore, the test should not have implications for other conditions or require cascade testing, unless family members are also indicated to start CBZ or OXC.

Test turnaround time (TAT) of *HLA-A*31:01* and *HLA-B*15:02* genotyping is reported to be approximately 5-7 days (per PICO). Testing must be conducted in a NATA accredited diagnostic laboratory in accordance with NPAAC guidelines. PASC noted in the PICO that drug hypersensitivity reactions are mostly delayed, occurring within 7-15 days of commencement of therapy. This would mean that there is a potentially safe therapeutic window where treatment is likely to be initiated prior to knowing genotyping outcomes in clinical practice. However, it is recommended that genotyping be conducted before, and not concurrently with treatment. The only condition in which delays to treatment may have important safety impacts is trigeminal neuralgia. Patients with this condition experience severe pain and require urgent commencement of therapy, and implementation of the intervention may have adverse impacts on safety due to

ongoing pain while waiting for genotyping results. This is a relatively small population, compared to the population sizes of the other conditions indicated for the drugs of interest (estimated in the PICO as between 1,140 to 2,120 incident trigeminal neuralgia cases per year, versus 16,000 cases of epilepsy).

False positive and false negative results are a potential risk of genotyping. The risk of both false positives and false negatives is expected to be negligible, as the test accuracy of genotyping methods in detecting the two variants has been well reported.^{3,4} However management in practice may result in a patient being unnecessarily changed to an alternative, possibly less effective, therapy even though they may not have suffered a drug hypersensitivity reaction despite a positive genotype result or a patient not receiving an alternative treatment experiencing CBZ or OXC-related hypersensitivity despite a negative genotype result. This is because although the probability of false positives and false negatives of the test result are low, not all patients with true positive results will develop CBZ or OXC-related hypersensitivity. Likewise, a true negative result does not always mean the patient will not develop CBZ or OXC-related hypersensitivity.

Also of note, in Chen et al. 2014's longitudinal analysis of a screening policy, adherence to screening and management protocols was low (nonadherent in 19.0%, and indeterminate in 54.6%). This included around 40% of patients being commenced on a non-CBZ therapy before the test result became available, which points to clinicians' real-world management pathway whereby genotyping policy may influence clinician's prescribing decisions in unintended ways, and health outcomes may partially be due to pre-emptive behaviour modification rather than response to testing results. Waiting for test results as indicated may not always occur, which may mean that patients, in practice, are unnecessarily changed to an alternative therapy in anticipation of test results.

12. Comparative effectiveness

Direct evidence

Two studies in Taiwan and Hong Kong examined the impact of policy or reimbursement of *HLA-B*15:02* genotyping prior to CBZ/other antiepileptic drug (AED) therapy using longitudinal clinical data pre- and post-introduction of policy/reimbursement.^{5,6} Results, interpretation, key uncertainties and GRADE assessments are presented in a Summary of Findings table (Table 4).

Both Chen et al. 2014 and Chang et al. 2023's results showed a significant relationship between implementation of policy for *HLA-B*15:02* genotyping prior to prescribing CBZ or other AEDs, and improved prescription practices and subsequent CBZ-related health outcomes.

A key strength of these studies is that they provide population-wide, longitudinal evidence of real-world use, prescription and subsequent health outcomes. However, there are some key issues with the study design, analysis and applicability to the Australian context:

1. These studies only include *HLA-B*15:02* genotyping policies in East Asian countries. *HLA-B*15:02* has a well-established significant association with both carrier frequencies and incidence of SCARs in East Asian populations (4.56% carrier rate versus 0.00–2.59% in

³ Buchner, A., Hu, X., & Aitchison, K. J. (2021). Validation of Single Nucleotide Variant Assays for Human Leukocyte Antigen Haplotypes *HLA-B*15:02* and *HLA-A*31:01* Across Diverse Ancestral Backgrounds. *Front Pharmacol*, 12, 713178

⁴ Jaruthamsophon, K., Sripo, T., Sukasem, C., & Limprasert, P. (2016). Comparison of a New In-House and Three Published *HLA-B*15:02* Screening Methods for Prevention of Carbamazepine-Induced Severe Drug Reactions. *PLOS ONE*, 11(5), e0155907.

⁵ Chang, B. L., Liu, J. R., Chang, S. H., & See, L. C. (2023). Impact on carbamazepine usage and cutaneous adverse reactions before and after the reimbursement of *HLA-B*15:02* genotyping in Taiwan, 2000–2017: A nationwide longitudinal study. *Epilepsia*, 64(10), 2679–2689. <https://doi.org/10.1111/epi.17726>

⁶ Chen, Z., Liew, D., & Kwan, P. (2014). Effects of a *HLA-B*15:02* screening policy on antiepileptic drug use and severe skin reactions. *Neurology*, 83(22), 2077–2084. <https://doi.org/10.1212/wnl.0000000000001034>

other biogeographical groups⁷). The intervention under consideration in this DCAR is both *HLA-A*31:01* and *HLA-B*15:02* genotyping in an Australian population with a unique ancestry mix, which is markedly more complex. Without Australian-specific data and/or direct evidence for *HLA-A*31:01* genotyping, it is difficult to draw conclusions on the efficacy of the proposed intervention in Australia.

2. For Chang et al. 2023, the number of episodes in each quarter included both new and existing CBZ users, and there was no sub-group analysis done for whether an episode was new or recurrent. “Episodes” are less likely to occur in the existing CBZ users as users are switched to alternative treatment if hypersensitivity occurs. Therefore, the reduction in incidence rates of SCARs and SJS-TEN are likely overestimated, as later quarters included both new and existing CBZ users.
3. For both studies, *HLA* testing rates or carrier status were not reported in association with outcomes. It was therefore a key assumption of the studies that improved outcomes post-implementation of screening policies were a result of use and adherence to *HLA* testing policies. However, in Chen et al. 2014, policy adherence was measured and was reportedly low (26.4%). Therefore, reductions in SCARs were likely a result of unintended changes to prescription practices brought on by the policy (e.g., preferential prescription of drugs that do not require testing due to consideration of factors such as alternative therapy availability, convenience, test turnaround time, and medico-legal issues). This is a key consideration for interpretation of direct evidence, and implementation of the intervention in practice.

⁷ Phillips, E. J., Sukasem, C., Whirl-Carrillo, M., et al.. (2018). Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. *Clin Pharmacol Ther*, 103(4), 574-581.

Table 4 Summary of findings table – direct from test to health outcomes evidence

Outcome	Participants and studies	Results, interpretation and key uncertainties	Certainty of the evidence (GRADE) Evidence statement
Change in management (CBZ and OXC use)	2 studies (retrospective longitudinal)	In Chen et al. 2014, following implementation of the <i>HLA-B*15:02</i> screening policy, the number of total new CBZ prescriptions decreased by 81.0% (from 10077 to 1910) and the number of total new OXC prescriptions decreased by 3.1% (from 384 to 372). There was a similar decrease in the number of prescriptions of CBZ which were for first-ever anti-epileptic drugs (AEDs) from 17.8% to 1.9% ($p<0.0001$). In Chang et al. 2023, the percentage of episodes ⁸ where the patient was not treated with either CBZ or OXC increased from approximately 93% in 2000 to 96% in 2017 following implementation of reimbursement for <i>HLA-B*15:02</i> genotyping. For CBZ, the genotyping rate was negatively correlated with the percentage of episodes where CBZ was used ($r=-.97$, $p<.0001$) and positively correlated with the percentage of episodes where CBZ was not used ($r=.95$, $p<.0001$). The direct evidence only included <i>HLA-B*15:02</i> genotyping policies in East Asian countries. Without Australian-specific data and/or direct evidence for <i>HLA-A*31:01</i> genotyping, it is difficult to draw conclusions on the efficacy of the proposed intervention in Australia.	 Low^a <i>HLA-B*15:02</i> prior to the commencement of CBZ or OXC compared to no genotyping may result in a large reduction in use of CBZ and may have little to no difference in use of OXC.
Incidence of SCARs	1 study (retrospective longitudinal)	The mean incidence rate of SCARs following reimbursement of <i>HLA-B*15:02</i> genotyping was significantly lower (1.65, 95% CI: 1.57–1.72) than before reimbursement (1.96, 95% CI not reported; $p<.0001$) following propensity score-based stabilized weighting. However, the reduction in incidence of SCARs was likely overestimated due to inclusion of both new and recurrent “episodes”.	 Very Low^b The evidence is very uncertain about the effect of genotyping for <i>HLA-A*31:01</i> and <i>HLA-B*15:02</i> prior to the commencement of CBZ or OXC compared to no genotyping on incidence of SCARs.
Incidence of SJS-TEN	2 studies (retrospective longitudinal)	In both Chen et al. 2014 and Chang et al. 2023, the incidence rate of CBZ-induced SJS-TEN episodes significantly decreased post <i>HLA-B*15:02</i> screening policy. However, these results may be mediated by non-adherence or unintended changes to prescription practice because of the genotyping policy (e.g., patients being started on antiepileptic drugs before receiving genotyping results, by clinicians preferentially commencing drugs that do not need genotyping).	 Low^a <i>HLA-A*31:01</i> and <i>HLA-B*15:02</i> prior to the commencement of CBZ or OXC compared to no genotyping may reduce incidence of CBZ-induced SJS-TEN episodes.

Abbreviations: AED=anti-epileptic drug; CI=confidence interval; DRESS=drug reaction with eosinophilia and systemic symptoms; HLA=human leukocyte antigen; MPE=maculopapular exanthema; CBZ=carbamazepine; OXC=oxcarbazepine; SCAR=severe cutaneous allergic reactions; SJS=Stevens–Johnson syndrome; TEN=toxic epidermal necrolysis.

- High risk of bias in both direct evidence studies (downgrade one of risk of bias). Direct evidence only for *HLA-B*15:02* genotyping policies in East Asian countries (downgrade one for indirectness).
- High risk of bias in direct evidence study (downgrade one of risk of bias). Direct evidence only for *HLA-B*15:02* genotyping policies in East Asian countries (downgrade one for indirectness). Likely overestimation of results due to inclusion of both new and recurrent episodes (downgrade one for imprecision).

Linked evidence

Linked evidence was identified for 24 studies (22 primary studies, one meta-analysis⁹ and one primary study with meta-analysis¹⁰) assessing the accuracy of genotyping for *HLA-A*31:01* and *HLA-B*15:02* prior to the commencement of CBZ or OXC compared to no pre-treatment genotyping. For pragmatism due to the volume of studies and to include only evidence most relevant to the intervention in this DCAR, only primary studies which genotyped both variants of interest were included (though results of “combined” genotyping of the 2 variants was not

required). However, any meta-analyses which genotyped one of the variants of interest was included for comprehensiveness.

Meta-analyses of primary studies identified in the literature was conducted. Key prognostic accuracy results (association between CBZ- and OXC-induced SCARs and variants of interest) are presented in Table . Only one study reported results for combined genotyping of the 2 variants (*HLA-A*31:01* and *HLA-B*15:02*) (but only for combined CBZ-induced SCARs in Chinese populations).

A summary of results, interpretation, key uncertainties and GRADE assessments are presented for linked evidence in Table . There was no linked evidence for change in management or health outcomes.

Table 5 Key linked evidence results of the association between CBZ- and OXC-induced SCARs and variants of interest (prognostic accuracy)†.

	Combined <i>HLA-A*31:01</i> and <i>HLA-B*15:02</i> ^a		<i>HLA-A*31:01</i> [*]		<i>HLA-B*15:02</i> [*]	
Outcome	N (k)	OR (95% CI), I ²	N (k)	OR (95% CI), I ²	N (k)	OR (95% CI), I ²
SCARs (combined)						
CBZ-induced SCARs (versus tolerant controls)						
Combined ancestry	-	-	5 (763)	3.8 (1.7–8.3), 55%†	5 (763)	5.4 (1.1–26.6), 80%†
European	-	-	2 (286)	3.8 (0.9–13.2), 56%	-	-
Asian	NR (1)	27.3 (10.4–71.5)^a, NR†	3 (477)	3.6 (1.1–11.7), 66%†	3 (477)	5.2 (0.7–37.2), 87%
OXC-induced SCARs (versus tolerant controls)						
Combined ancestry	-	-	-	-	-	-
European	-	-	-	-	2 (361)	1.4 (0.1–25.3), 75%
Asian	-	-	-	-	-	-
Individual SCARs						
CBZ-induced DRESS (versus tolerant controls)						
Combined ancestry	-	-	6 (711)	18.6 (9.8–35.2), 0%†	-	-
European	-	-	3 (387)	39.8 (13.3–119.1), 0%†	-	-
Asian	-	-	3 (324)	12.5 (5.7–27.5), 0%†	-	-
OXC-induced DRESS (versus tolerant controls)						
Combined ancestry	-	-	-	-	-	-

⁸ An episode was defined as where a patient had ≥2 outpatient visits or ≥1 hospitalisation due to epilepsy or neuralgia within a calendar quarter (Chang et al. 2023).

⁹ Nicoletti, P., Barrett, S., McEvoy, L., et al.. (2019). Shared Genetic Risk Factors Across Carbamazepine-Induced Hypersensitivity Reactions. *Clinical Pharmacology and Therapeutics*, 106(5), 1028-1036. 3

¹⁰ Genin, E., Chen, D. P., Hung, S. I., et al.. (2014). *HLA-A*31:01* and different types of carbamazepine-induced severe cutaneous adverse reactions: an international study and meta-analysis. *The Pharmacogenomics Journal*, 14(3), 281-288.

European	-	-	-	-	-	-
Asian	-	-	-	-	-	-
CBZ-induced SJS-TEN (versus tolerant controls)						
Combined ancestry	-	-	9 (1438)	1.9 (1.01–3.5), 0%†	9 (1286)	31.3 (16.7–58.4), 51%†
European	-	-	3 (398)	3.5 (1.1–11.3), 0%†	2 (184)	44.2 (6.0–327.5), 0%†
Asian	-	-	6 (1040)	1.5 (0.7–3.1), 8%	7 (1102)	30.4 (15.1–61.6), 63%†
OXC-induced SJS-TEN (versus tolerant controls)						
Combined ancestry	-	-	-	-	-	-
European	-	-	-	-	-	-
Asian	-	-	-	-	-	-
CBZ-induced MPE (versus tolerant controls)						
Combined ancestry	-	-	5 (844)	5.3 (2.5–11.0), 0%†	4 (815)	0.92 (0.6–1.5), 0%
European	-	-	-	-	-	-
Asian	-	-	4 (731)	4.5 (1.9–10.5), 0%†	3 (702)	0.92 (0.6–1.5), 0%
OXC-induced MPE (versus tolerant controls)						
Combined ancestry	-	-	-	-	-	-
European	-	-	-	-	-	-
Asian	-	-	3 (260)	1.5 (0.6–4.0), 13%	3 (260)	0.7 (0.2–3.1), 0%

Abbreviations: CBZ=carbamazepine; CI=confidence interval; DRESS=drug reaction with eosinophilia and systemic symptoms; HLA=human leukocyte antigen; k=number of studies; MPE=maculopapular exanthema; N=number of participants total; OXC=oxcarbazepine; SCAR=severe cutaneous allergic reactions; SJS=Stevens–Johnson syndrome; TEN= toxic epidermal necrolysis.

† Significant results presented in **bold**.

^ Results of combined *HLA-A*31:01* and *HLA-B*15:02* genotyping (Chinese population only) from Genin et al. (2014)¹⁰.

* Results of meta-analysis of primary studies where both *HLA-A*31:01* and *HLA-B*15:02* genotyping was conducted, but results were presented separately. Conducted as part of DCAR.

a. Chinese population only.

Table 6 Summary of findings table – linked evidence of test accuracy

Outcome	Participants and studies	Results, interpretation and key uncertainties	Certainty of the evidence (GRADE) Evidence statement
Cross-sectional accuracy	-	No studies were identified which reported the cross-sectional accuracy for combined <i>HLA-A*31:01</i> and <i>HLA-B*15:02</i> genotyping specifically, however, the technical methods for genotyping have well-established accuracy.	-
Diagnostic yield	3 studies; N>38654 (N in Park et al. 2016 ¹¹ not specified)	The frequency of <i>HLA-B*15:02</i> and <i>HLA-A*31:01</i> variants vary based on ancestry. The best estimates are from aggregated data presented as part of CPIC guidelines based on biogeographical groups. Recent data identified in the review largely supports these estimates, however, lack of reported ancestry in one key study from the USA limits synthesis of information. There were no available studies from the Australian population reporting the prevalence of <i>HLA-A*31:01</i> or <i>HLA-B*15:02</i> variants. With Australia's cultural diversity and unique ancestry make-up, there are serious applicability issues of reported variant frequencies which will directly affect the efficacy of testing and subsequent clinical outcomes.	⊕⊕⊕⊕ Very Low^a The evidence is very uncertain about the diagnostic yield of <i>HLA-A*31:01</i> and <i>HLA-B*15:02</i> genotyping prior to the commencement of CBZ or OXC compared to no genotyping.
Prognostic accuracy	Combined <i>HLA-A*31:01/HLA-B*15:02</i> genotyping for SCARs (combined) in Chinese populations 1 study; N=135	Overall, there was a statistically significant association between Combined <i>HLA-A*31:01</i> and <i>HLA-B*15:02</i> genotyping and CBZ-induced SCARs (OR=27.3; 95% CI 10.4–71.5) in Chinese populations ¹⁰ .	⊕⊕⊕⊕ Very low^b The evidence is very uncertain about the impact of <i>HLA-A*31:01</i> and <i>HLA-B*15:02</i> genotyping prior to the commencement of CBZ or OXC compared to no genotyping on the incidence of SCARs.
	Studies where both <i>HLA-A*31:01</i> and <i>HLA-B*15:02</i> genotyping was conducted, but results were presented separately SCARs (combined) (11 studies, 0 with meta-analysis) DRESS (9 studies, 2 with meta-analysis)	SCARs (combined): Overall, there was a statistically significant association between <i>HLA-A*31:01</i> and CBZ-induced SCARs (OR=3.79; 95% CI 1.72 to 8.33; N=763). Significance was also seen in the European ancestry subgroup, but not the Asian ancestry subgroup. All pooled results had significant heterogeneity ($I^2=55-66\%$), though point estimates and 95% CI boundaries mostly did not cross the direction of effect threshold, suggesting consistency. Meta-analysis of OXC-induced SCARs was not possible as only one study reported results for both cases and tolerant controls. Overall, there was a statistically significant association between <i>HLA-B*15:02</i> and CBZ-induced SCARs (OR=5.43; 95% CI 1.11 to 26.62; N=763). There was no difference in the Asian ancestry subgroup, and meta-analysis was not possible in the European subgroup. All pooled results showed considerable heterogeneity ($I^2=80-87\%$), and 95% CI boundaries mostly crossed the direction of effect threshold, suggesting inconsistency. There was also no significant association between <i>HLA-B*15:02</i> and OXC-induced SCARs in two studies with Asian ancestry (OR=1.37; 95% CI 0.07 to 25.29; N=361), with significant heterogeneity in pooled results ($I^2=75\%$). There were no studies with European ancestry.	⊕⊕⊕⊕ Low^c <i>HLA-A*31:01</i> and <i>HLA-B*15:02</i> prior to the commencement of CBZ or OXC compared to no genotyping may predict the incidence of SCARs, especially for specific SCARs in specific ethnicities.

¹¹ Park, H. J., Kim, Y. J., Kim, D. H. et al. (2016). HLA allele frequencies in 5802 Koreans: Varied allele types associated with SJS/TEN according to culprit drugs. *Yonsei Medical Journal*, 57(1), 118-126

	SJS-TEN (12 studies, 2 with meta-analysis) MPE (10 studies, 0 with meta-analysis)	DRESS: In meta-analysis of primary studies, there was a significant association between CBZ-induced DRESS and <i>HLA-A*31:01</i> overall (OR=18.58; 95% CI 9.80 to 35.19; N=711) and in European and Asian populations individually with no heterogeneity ($I^2=0\%$). These results were supported by meta-analyses from the literature.^{13 14}. There was no association between <i>HLA-B*15:02</i> and CBZ- or OXC-induced DRESS (N=517). None of the 86 CBZ-induced cases from pooled primary results had this variant; only one of the six OXC-induced cases did (compared to 7.9% (8/101) of the tolerant controls). Neither meta-analysis from the literature examined this association. SJS-TEN: In meta-analysis of primary studies, there was a significant association between CBZ-induced SJS-TEN and <i>HLA-A*31:01</i> overall (OR=1.87, 95% CI 1.01 to 3.45; N=1438) and in European populations (OR=3.46, 95% CI 1.06 to 11.29; N=398), with no heterogeneity ($I^2=0\%$), however point estimates and 95% CI boundaries generally sat on different sides of the direction of effect threshold, suggesting inconsistency. The two meta-analyses from the literature reported similar results (one significant and one non-significant for European populations). For <i>HLA-B*15:02</i>, there was a significant association with CBZ-induced SJS-TEN cases for the total population (OR=31.27; 95% CI 16.73 to 58.44; N=1286) and both European and Asian ancestry subpopulations in the meta-analysis of primary studies. While there was significant statistical heterogeneity ($I^2=51-63\%$), all point estimates and 95% CIs indicated an appreciable effect. Neither meta-analysis from the literature examined this association. MPE: In meta-analysis of primary studies, there was a significant association between CBZ-induced MPE and <i>HLA-A*31:01</i> overall (OR=5.26; 95% CI 2.52 to 10.99; N=844). For <i>HLA-B*15:02</i>, there was no statistical difference between the two cohorts (OR=0.92; 95% CI 0.56 to 1.54; N=815). For both, notable heterogeneity was not detected ($I^2=0\%$), with general overlap of CIs and directions of effect of point estimates. For OXC-induced MPE, there was no significant association with <i>HLA-A*31:01</i> or <i>HLA-B*15:02</i> (N=260), with low or no heterogeneity ($I^2=0-13\%$).	
Test accuracy	Combined <i>HLA-A*31:01/HLA-B*15:02</i> genotyping for SCARs (combined – DRESS and SJS-TEN) in Chinese populations 1 study	Genin et al. 2014 was the only study to report results of combined <i>HLA-A*31:01/HLA-B*15:02</i> genetic screening, and only for Chinese populations. Results showed an estimated sensitivity of 74.6% and specificity of 90.3% of combined <i>HLA-A*31:01/HLA-B*15:02</i> genotyping. The addition of <i>HLA-A*31:01</i> to <i>HLA-B*15:02</i> testing would reportedly reduce the number needed to test (NNT) to prevent one case of CBZ-induced SCARs from 527 to 455. However, the number of patients denied CBZ inappropriately would increase from 53 to 94 in 1000 screened. Despite the low estimated PPV of combined <i>HLA-A*31:01</i> and <i>HLA-B*15:02</i> test (2.3% for CBZ-induced SCARs), genotyping may be worthwhile considering (a) there are effective alternative treatments to CBZ which can be used; and (b) the high morbidity and mortality of SCARs. Importantly, the effectiveness of pre-treatment genotyping will be based on frequencies of both <i>HLA-A*31:01/HLA-B*15:02</i> in the population of interest.	⊕⊕⊕⊕ Very low^b The evidence is very uncertain about the impact of <i>HLA-A*31:01</i> and <i>HLA-B*15:02</i> genotyping prior to the commencement of CBZ or OXC compared to no genotyping on diagnostic accuracy of SCARs (combined).
	<i>HLA-A*31:01</i> genotyping for DRESS (1 study with meta-analysis) in	DRESS: Results showed an estimated sensitivity of 70.0% and 50.0%, and specificity of 96.1% and 95.8% of <i>HLA-A*31:01</i> genotyping to prevent CBZ-induced DRESS in European and Chinese populations, respectively, versus tolerant controls¹⁰. Estimates showed that NNT to prevent one case of CBZ-induced	⊕⊕⊕⊕ Very low^b The evidence is very uncertain about the impact of <i>HLA-A*31:01</i> genotyping prior to the

Chinese and European populations	DRESS would be 3334 (European populations) and 5000 (Chinese populations). However, the number of patients denied CBZ inappropriately would be between 38 to 44 (European populations) and 36 to 41 (Chinese populations) in 1000 screened.	commencement of CBZ or OXC compared to no genotyping on diagnostic accuracy of specific SCARs.
<i>HLA-B*15:02</i> genotyping for SJS-TEN (2 studies with meta-analysis) in Chinese populations	<u>SJS-TEN</u> : In Chinese populations only, the number needed to test to prevent one case of CBZ-induced DRESS would be 527; however, the number of patients denied CBZ inappropriately would be between 53 in 1000 screened ¹ . Across two studies, sensitivity was reported as 69.6–77.4%; specificity was 84.4–94.4% ^{1,12} .	

Abbreviations: CBZ=carbamazepine; CI=confidence interval; DRESS=drug reaction with eosinophilia and systemic symptoms; HLA=human leukocyte antigen; k=number of studies; MPE=maculopapular exanthema; N=number of participants total; NNT=number needed to test; OXC=oxcarbazepine; SJS=Stevens–Johnson syndrome; TEN= toxic epidermal necrolysis.

- Lack of reported ancestry in one key study from the USA (downgrade one for imprecision). No Australian studies or estimates based on of Australian ancestry proportions which is a key determinant of diagnostic yield (downgrade two for indirectness).
- High risk of bias for included study (downgrade one for risk of bias). Small sample size; results from only one included study (downgrade one for imprecision). For Chinese population only, so does not extrapolate to Australian population ancestral make-up (downgrade one for indirectness).
- High risk of bias across many studies (downgrade one of risk of bias). No Australian studies or studies with similar ancestral make-up to Australia (downgrade one for indirectness).

Clinical claim

The use of *HLA-A*31:01* and *HLA-B*15:02* genotyping prior to the commencement of carbamazepine or oxcarbazepine compared to no pre-treatment genotyping results in superior effectiveness in terms of predicting carbamazepine- or oxcarbazepine-related drug hypersensitivity compared with no pre-treatment genotyping.

The use of *HLA-A*31:01* and *HLA-B*15:02* genotyping before the commencement of carbamazepine or oxcarbazepine results in noninferior safety compared with no pre-treatment genotyping. While the probability of test-related false positive and false negatives are low, clinical management in practice may result in patients with positive genotypes who may not actually be at risk of drug hypersensitivity reactions being unnecessarily changed to an alternative, possibly less effective therapy and patients with negative genotypes not receiving an alternative treatment who are still at risk of drug hypersensitivity reactions. This is because not all patients testing positive for the genotypes will be at increased risk of drug hypersensitivity reactions and not all patients testing negative for the genotypes will have no risk of drug hypersensitivity reactions.

There is insufficient evidence to determine the effectiveness of combined *HLA-A*31:01* and *HLA-B*15:02* genotyping prior to the commencement of carbamazepine or oxcarbazepine compared to no pre-treatment genotyping for:

- improving outcomes of overall survival, morbidity or mortality, OR
- preventing carbamazepine- or oxcarbazepine-related drug hypersensitivity (from treatment switching). However, there is evidence that implementation of policies for *HLA-B*15:02* only genotyping prior to the commencement of carbamazepine in East Asian populations reduces carbamazepine prescription, which may reduce the incidence of SCARs. However, in Chen et al. 2014, policy adherence was reportedly low (26.4%), with 40% of patients commenced on a non-CBZ therapy before the test result became available, meaning causality cannot be ascertained.

¹² Shi, Y. W., Min, F. L., Zhou, D., et al. (2017). *HLA-A*24:02* as a common risk factor for antiepileptic drug-induced cutaneous adverse reactions. *Neurology*, 88(23), 2183-2191.

13. Economic evaluation

Based on the clinical claim of superior effectiveness in terms of predicting carbamazepine- or oxcarbazepine-related drug hypersensitivity compared with no pre-treatment genotyping, a CEA (cost per patient with a *HLA-A*31:01* and *HLA-B*15:02* variant identified and cost per patient regarding severe drug hypersensitivity reactions avoided), and a CUA (cost per quality-adjusted life years (QALY) gained) were conducted. Table 7 provides a brief overview of the model parameters.

Table 7 Summary of the economic evaluation

Component	Description
Perspective	Health care system perspective
Population	Patients who are about to commence CBZ or OXC treatment for the first time.
Prior testing	NA
Comparator	No testing
Type(s) of analysis	CEA and CUA
Outcomes	- Number of patients with positive genotyping result (i.e. <i>HLA-A*31:01</i> and/or <i>HLA-B*15:02</i> variant identified). - Number of patients with severe drug hypersensitivity reactions (SJS-TEN/DRESS) avoided. - QALYs gained (for epilepsy) - Difference in pain-controlled patient (for TN)
Time horizon	Short-term: 3 months Long-term: lifetime (for epilepsy); 10 years (for TN)
Computational method	Decision tree model and Markov model
Generation of the base case	Modelled
Health states	Decision tree terminal states: - No CBZ/OXC-induced SJS-TEN/DRESS – CBZ/OXC treatment continued - CBZ/OXC-induced SJS-TEN/DRESS – alternative treatment - Carriers identified by <i>HLA-A*31:01</i> and/or <i>HLA-B*15:02</i> genotyping – alternative treatment Health states in the Markov model (for epilepsy): - Uncontrolled epilepsy - Remission - Death Health states in the Markov model (for TN): - Uncontrolled pain - Controlled pain - Death
Age	5 (average age at diagnosis 4.3 years) (Berg et al., 2012 ¹³). However age was not explicitly included in the model as there were no variables that differed by age
Cycle length	1 year with half-cycle correction

¹³ Berg, A. T., Zelko, F. A., Levy, S. R., and Testa, F. M. (2012). Age at onset of epilepsy, pharmacoresistance, and cognitive outcomes: a prospective cohort study. *Neurology*, 79(13), 1384-1391.

Component	Description		
Transition probabilities	All transition probabilities were from the clinical evidence (Section 2), published literature and assumptions:		
	Parameter	Value	Source
	For both indications		
	Probability of death due to CBZ/OXC-induced SJS-TEN/DRESS	0.1114	Calculated estimate (detailed calculation presented in Section 3A.2.4)
	Probability of people who carry at least one of the <i>HLA-A*31:01</i> and <i>HLA-B*15:02</i> alleles	0.0563	Calculated estimate (detailed calculation presented in Section 3A.2.4)
	PPV	0.0077	Calculated estimate (detailed calculation presented in Section 3A.2.4)
	Probability of CBZ/OXC-induced SJS-TEN/DRESS among non-carriers of <i>HLA-A*31:01</i> and <i>HLA-B*15:02</i> alleles	0.0239	Calculated estimate (detailed calculation presented in Section 3A.2.4)
	Probability of CBZ/OXC-induced SJS-TEN/DRESS	2.3%	The studies (identified in Section 2) had a range of between 2.3% and 25% of patients having a SCAR reaction. The 2.3% was used in the model aligning with the overall estimate of hypersensitivity reactions highlighted in the PICO (ratified PICO).
	Proportion of prescribed CBZ	0.8722	Assumed that all patients entering into the model receiving either CBZ or OXC unless alternative treatment applied due to hypersensitivity reactions. Pharmaceutical Benefits Schedule Item Reports – Requested PBS Items processed from July 2023 to June 2024 (Services Australia, 2024) (detailed calculation presented in Section 3A.2.4)
	Proportion of prescribed OXC	0.1278	Assumed that all patients entering into the model receiving either CBZ or OXC unless alternative treatment applied due to hypersensitivity reactions. 1-proportion of prescribed CBZ (0.8722)=0.1278
	For epilepsy		
	Probability of death due to epilepsy	0.00065	Assumed same as the general population. Patients entering the model at age 5 with a life expectancy of 83 (Australian Bureau of Statistics, 2018-2020).
	Probability of death among patient who has remission from epilepsy	0.00065	Assumed the same as probability of death due to epilepsy in Australia. This assumption is also consistent with the standardised mortality of remission (i.e., 1.000) used in the study by Plumpton 2015 ¹⁴ (0.00065 *1=0.00037).

¹⁴ Plumpton, C. O., Yip, V. L., Alfirevic, A., et al. 2015a. Cost-effectiveness of screening for *HLA-A*31:01* prior to initiation of carbamazepine in epilepsy. *Epilepsia*, 56(4), 556-563

Component	Description		
	Probability of death due to uncontrolled epilepsy	0.0013325	Assumed equivalent to the standardised mortality rate for chronic epilepsy, uncontrolled seizures (Plumpton 2015) ($0.00065 \times 2.05 = 0.0013325$).
	Probability of patients treated with CBZ/OXC transitioned from uncontrolled epilepsy to remission	0.7017	Percentage of 12-month remission of CBZ (254/362) from the SANDA study which was an unblinded RCT in hospital-based outpatient clinics in the UK (Marson et al., 2007 ¹⁵).
	Probability of patients treated with VPA transitioned from uncontrolled epilepsy to remission	0.5824	The HR of remission with VPA compared to CBZ was 0.83, that was $0.7017 \times 0.83 = 0.5824$ (Marson et al., 2007; Plumpton et al., 2015)
	For TN		
	Probability of patients treated with CBZ/OXC transitioned from uncontrolled pain to controlled pain	0.9	Expert opinion on pain relief of 1 st line treatments on TN (email contact)
	Probability of patients treated with PBG/GPB transitioned from uncontrolled pain to controlled pain	0.5	Expert opinion on pain relief of 2 nd line treatments on TN (email contact)
	Proportion of prescribed GPB	0.9640	Pharmaceutical Benefits Schedule Item Reports – Requested PBS Items processed from July 2023 to June 2024 (Services Australia, 2024 ¹⁶) (detailed calculation presented in Section 3A.2.4)
	Proportion of prescribed PGB	0.0360	Pharmaceutical Benefits Schedule Item Reports – Requested PBS Items processed from July 2023 to June 2024 (Services Australia, 2024) (detailed calculation presented in Section 3A.2.4)
	Probability of death of general population	0.00065	Patients entering the model at age 5 with a life expectancy of 83 (Australian Bureau of Statistics, 2018-2020 ¹⁷).
Discount rate	5% for both costs and QALYs		
Software	Excel and TreeAge Pro		

Abbreviations: CBZ= carbamazepine; CEA=cost-effectiveness analysis; CUA=cost-utility analysis; DRESS= drug reaction with eosinophilia and systemic symptoms; GPB= gabapentin; OXC=oxcarbazepine; PBG= Pregabalin; PPV= Positive predict value; QALYs=Quality Adjusted Life Years; SJS= Stevens–Johnson syndrome; TEN= toxic epidermal necrolysis; TN= trigeminal neuralgia; VPA= Valproate.

¹⁵ Marson, A. G., Al-Kharusi, A. M., Alwaidh, M., et al. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet*, 369(9566), 1000-1015.

¹⁶ Services Australia. (2024). Pharmaceutical Benefits Schedule Item Reports. Australian Government. http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp

¹⁷ Australian Bureau of Statistics. (2018-2020). Life tables. ABS. <https://www.abs.gov.au/statistics/people/population/life-expectancy/2018-2020>

The model was conducted using a stepped approach in light of the absence of robust test to outcomes evidence. Step 1 considered the cost per patient with positive genotyping results (i.e. *HLA-A*31:01* and/or *HLA-B*15:02* variant identified). Step 2 considered the probabilities of treatment-induced (CBZ/OXC-induced) severe hypersensitivity reactions (SJS-TEN/DRESS) in carriers and non-carriers of *HLA-A*31:01* and *HLA-B*15:02* alleles. At this point the impacts of false-positive and false-negative *HLA* genotyping were considered in the model. While specific pathways for false positives and false negatives were not developed, the costs and outcomes for patients were incorporated into the model as patients are treated as they would be in practice. This approach is consistent with the recently published guidance for economic evaluations of genetic medicine (Vellekoop et al., 2021¹⁸). Step 3 considered the additional costs associated with treating epilepsy, trigeminal neuralgia (TN) and SJS-TEN/DRESS, and transition probabilities between health states of epilepsy and TN. Each economic model consisted of two models: the decision tree and Markov model. In the decision tree, there were two arms: 1) *HLA-A*31:01* and *HLA-B*15:02* genotyping; 2) no testing. In the Markov model, for epilepsy (Figure 22), the health states were: 1) uncontrolled epilepsy; 2) remission; 3) death; for TN, the health states were: 1) uncontrolled pain; 2) controlled pain; 3) death. The results are presented in Table .

In summary, when only considering the cost of *HLA-A*31:01* and *HLA-B*15:02* genotyping (\$188), the cost per patient with positive genotyping results was \$3,337.68. The cost per patient avoiding SJS-TEN/DRESS was \$428,125.68, when standard and alternative treatment costs were added. When considering the costs of treatments and associated costs relating to hospitalisations and hypersensitivity reactions, compared to no testing, genotyping was less costly and more effective for epilepsy (dominant), but less costly and less effective for TN.

¹⁸ Vellekoop, H., Huygens, S., Versteegh, M., et al. (2021). Guidance for the Harmonisation and Improvement of Economic Evaluations of Personalised Medicine. *PharmacoEconomics*, 39(7), 771-788

Table 8 Results of the stepped economic analysis

Step	HLA-A*31:01 and HLA-B*15:02 genotyping	No testing	Increment	ICER
Step 1 – Cost per patient with positive genotyping results				
Costs	\$188	\$0	\$188	\$3,337.68
Outcome 1 (Number of patients with positive genotyping results)	0.0563	0	0.0563	
Step 2 – Cost per patient regarding severe drug hypersensitivity reactions avoided				
Costs	\$316.79	\$131.13	\$185.66	\$428,125.68
Outcome 2 (Number of patients with SJS-TEN/DRESS; the difference in patients avoiding SJS-TEN/DRESS)	0.02257	0.023	0.000434	
Step 3 – Cost per QALY (for epilepsy)				
Costs	\$76,727.89	\$76,842.47	-\$114.58	Genotyping is a dominant strategy
Outcome 3 (QALY)	16.11853	16.11826	0.00027	
Step 3 – Cost per pain-controlled case (for TN)				
Costs	\$16,418.01	\$16,465.61	-\$47.61	\$712.06
Outcome 3 (QALY)	8.7653	8.8322	-0.0669	

Abbreviations: DRESS= drug reaction with eosinophilia and systemic symptoms; ICER=Incremental cost-effectiveness ratio; QALY=quality-adjusted life year; SJS= Stevens–Johnson syndrome; TEN= toxic epidermal necrolysis; TN= trigeminal neuralgia. Note: Multiple outcomes may be informative for MSAC decision making-within each step.

The key drivers (top five parameters) from the one-way sensitivity analysis are presented in Table 9.

Table 9 Key drivers of the model

Description	Method/Value	Impact Base case: <i>HLA-A*31:01</i> and <i>HLA-B*15:02</i> is a dominant strategy
Annual cost of remission from epilepsy in patients treated with CBZ/OXC without SJS-TEN/DRESS	According to a recent systematic review (Begley & Durgin, 2015 ¹⁹). In the analysis by Foster 2020 (Foster et al., 2020 ²⁰), it was assumed that the direct health care costs for people with uncontrolled epilepsy were 10 times those of people with controlled epilepsy. Thus, this value was assumed to be one tenth of the annual cost of uncontrolled epilepsy treated with CBZ/OXC without SJS-TEN/DRESS.	High, favours genotyping when this value increased.
Annual cost of remission from epilepsy in patients treated with VPA without SJS-TEN/DRESS	According to a recent systematic review (Begley & Durgin, 2015). In the analysis by Foster 2020 (Foster et al., 2020), it was assumed that the direct health care costs for people with uncontrolled epilepsy were 10 times those of people with controlled epilepsy. Thus, this value was assumed to be one tenth of the annual cost of uncontrolled epilepsy treated with VPA without SJS-TEN/DRESS.	High, favours no testing when this value increased.
Probability of death due to CBZ/OXC-induced SJS-TEN/DRESS	Calculated estimate (detailed calculation presented in Section 3A.2.4)	High, favours genotyping when this value increased.
Annual cost of remission from epilepsy in patients treated with VPA with SJS-TEN/DRESS	The sum of annual cost of remission treated with VPA without SJS-TEN/DRESS and the cost of hospitalisation for SJS-TEN/DRESS.	High, favours genotyping when this value increased.
Probability of death due to epilepsy	Assumed same as the general population. Patients entering the model at age 5 with a life expectancy of 83 (Australian Bureau of Statistics, 2018-2020).	High, favours genotyping when this value increased.

Abbreviations: CBZ= carbamazepine; DRESS= drug reaction with eosinophilia and systemic symptoms; HLA = human leukocyte antigen; OXC=oxcarbazepine; PPV= Positive predict value; SJS= Stevens–Johnson syndrome; TEN= toxic epidermal necrolysis; VPA= Valproate

The results of key univariate sensitivity analysis (one-way sensitivity analysis) are summarised below (Table 10), using the top driver (i.e., Annual cost of remission treated with CBZ/OXC without SJS-TEN/DRESS) for epilepsy as an example. The tornado diagram and ICER scatterplot are provided in Figures 1 and 2.

¹⁹ Begley, C. E., & Durgin, T. L. (2015). The direct cost of epilepsy in the United States: A systematic review of estimates. *Epilepsia*, 56(9), 1376-1387.

²⁰ Foster, E., Chen, Z., Zomer, E., et al. (2020). The costs of epilepsy in Australia: A productivity-based analysis. *Neurology*, 95(24), e3221-e3231

Table 10 Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case	-\$114.58	0.00027	-\$424,370.37 (Genotyping less costly and more effective)
Annual cost of remission treated with CBZ/OXC without SJS-TEN/DRESS (base case \$1,822.87; $\pm 20\%$)			
\$1,458.30	\$269.87	0.00027	\$985,632.75 (Genotyping more costly and more effective)
\$2,187.45	-\$499.04	0.00027	-\$1,822,628.10 (Genotyping far less costly and more effective)

These results are largely dependent on clinical evidence that, as discussed in the previous section do not fully support the claim of clinical effectiveness in reducing drug-related hypersensitivity reactions. Additionally, the evidence regarding the allele frequencies of *HLA-A31:01* and *HLA-B15:02* across different population groups is not robust. Therefore, the interpretation of the cost-effectiveness evidence should be approached with caution. In addition, to estimate the cost of hospitalisation, AR-DRG codes were identified that could be considered related to the skin hypersensitivity reactions. Costs associated with AR-DRG code J68A Major Skin Disorders, Major Complexity were considered the most appropriate but as with all AR-DRG codes, the resulting costs are meant to only serve as an approximation to the actual costs that may be incurred given the very specific hypersensitivity reactions being costed here.

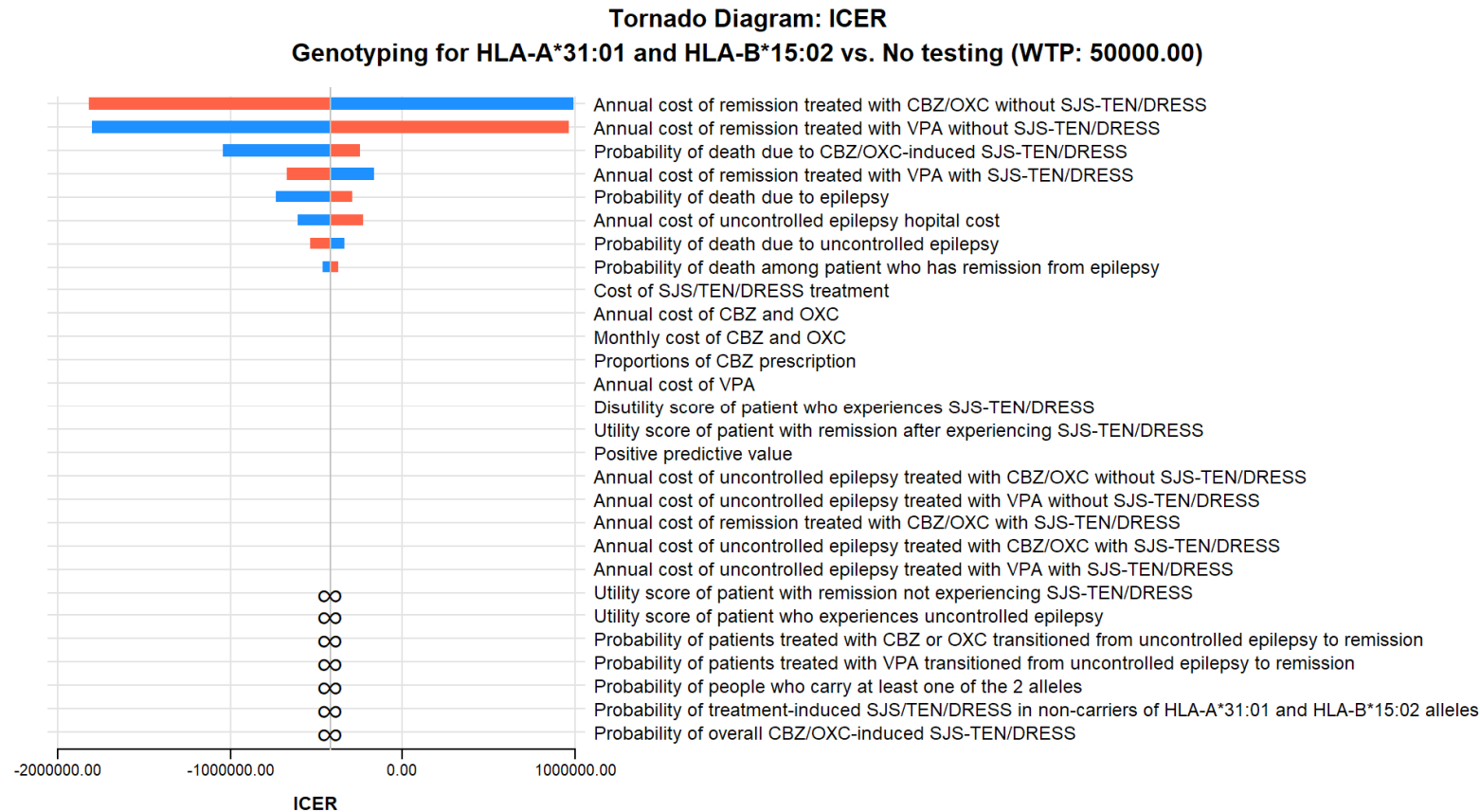


Figure 1 Tornado diagram for one-way sensitivity analysis for epilepsy

For each bar, the blue portion represents the part of the input range from the lower bound to the base case value, while the red portion represents the part of the input range from the base case value to the upper bound.

Abbreviations: CBZ=carbamazepine; DRESS=drug reaction with eosinophilia and systemic symptoms; HLA=human leukocyte antigen; ICER=Incremental cost-effectiveness ratio; OXC=oxcarbazepine; SJS=Stevens–Johnson syndrome; TEN= toxic epidermal necrolysis; VPA= Valproate.

ICE Scatterplot, No testing vs. Genotyping for HLA-A*31:01 and HLA-B*15:02

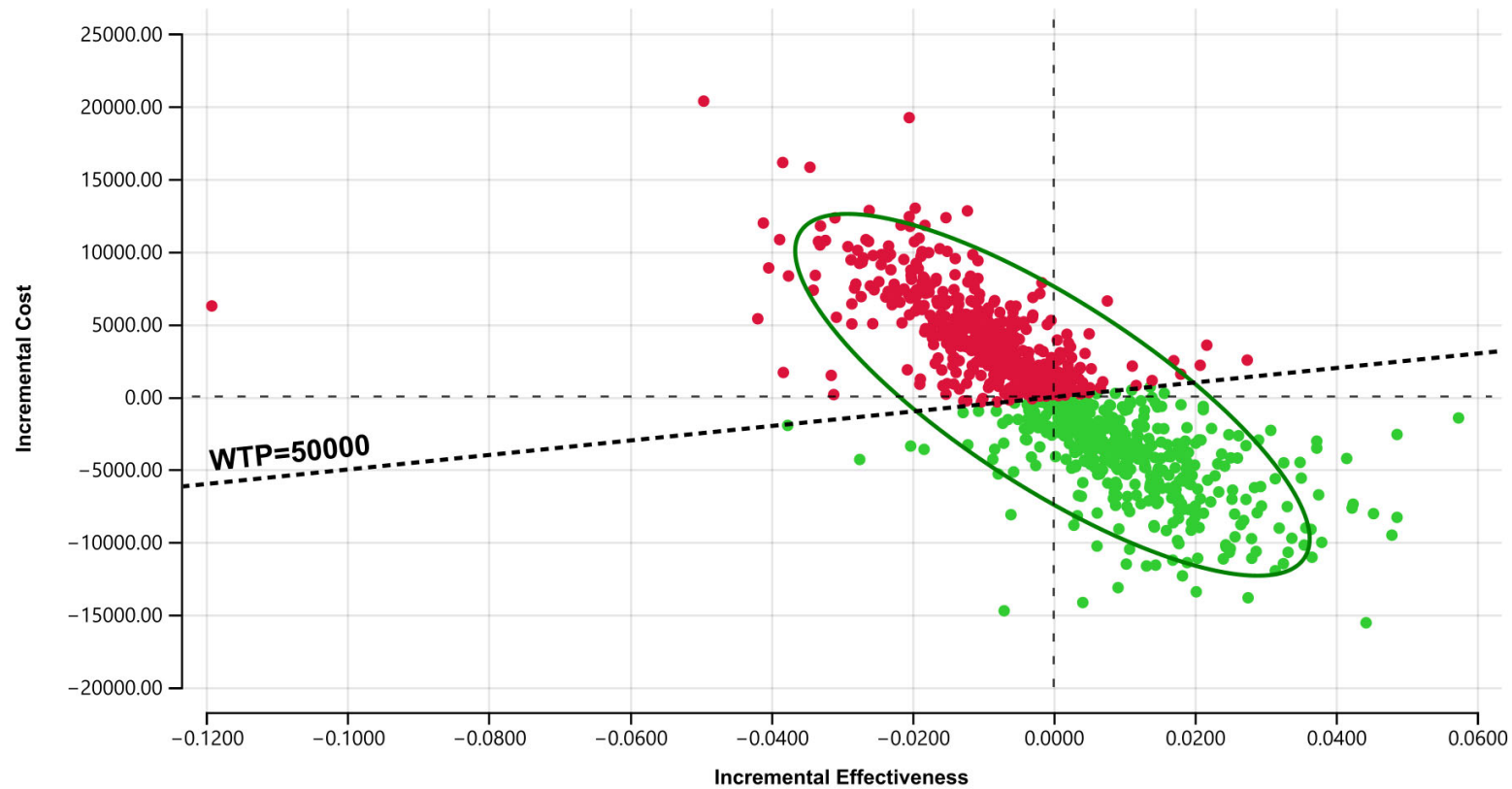


Figure 2 Cost-effectiveness scatterplot for probability sensitivity analysis for epilepsy

The model calculations which favour no testing are shown in green, whilst those model calculations which favour the genotyping strategy are shown in red. Note: WTP is only for reference not for decision-making. Abbreviations: ICE=incremental cost-effectiveness; HLA=human leukocyte antigen; WTP=willingness to pay.

Amendments to the economic evaluation

ESC requested a revised economic evaluation because of errors due to the incorrect entry of input variables in the epilepsy model which also affected the appropriateness of the previous model's structure. The applicant's pre-ESC response also identified a costing error in the TN model due to the same annual cost (\$524.51) being used for the treatment of epilepsy and trigeminal neuralgia, Post-ESC, the economic evaluations for epilepsy and TN were revised.

The structure of the previous model is presented in **Figure 3**.

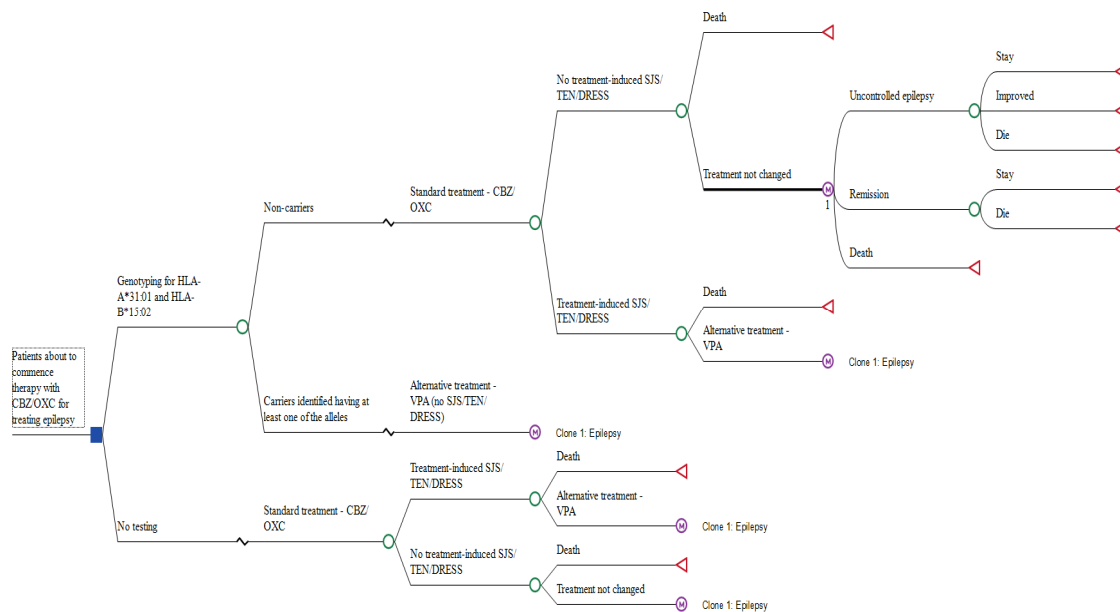


Figure 3 Original economic model (decision tree + Markov model) of pre-treatment HLA-A*31:01 and HLA-B*15:02 genotyping for patients about to commence therapy with CBZ and OXC for epilepsy

The structure of the revised model for epilepsy is presented in **Figure 4**.

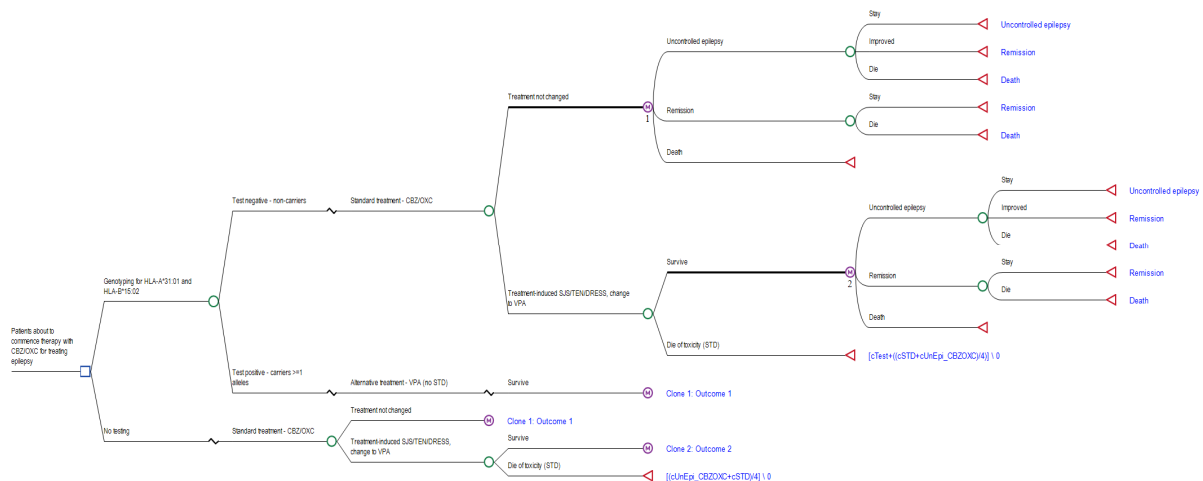


Figure 4 Revised economic model (decision tree + Markov model) of pre-treatment HLA-A*31:01 and HLA-B*15:02 genotyping for patients about to commence therapy with CBZ and OXC for epilepsy

Key changes in the revised economic model were as follows:

- The decision tree was modified based on feedback from the ESC discussant.
- The model was changed to incorporate half cycle corrections
- The model variables were cleaned up (unused variables removed) to make the model easier to validate (no effect on the model)

The revised model estimated a cost per QALY gained for epilepsy from HLA-A*31:01 and HLA-B*15:02 genotyping of \$825,763. In addition, the ICER from HLA-A*31:01 and HLA-B*15:02 genotyping of TN patients was found to be dominated on a cost per pain controlled case measure (see Table 11 which omits Steps 1 and 2 which report similar values as Table 8 but includes the previous values for Step 3 from Table 8 for comparison).

Table 11 Results of the stepped economic analysis

Step	HLA-A*31:01 and HLA-B*15:02 genotyping	No testing	Increment	ICER
Step 3 from original model – Cost per QALY (for epilepsy)				
Costs	\$76,727.89	\$76,842.47	-\$114.58	Genotyping is a dominant strategy (Genotyping less costly and slightly more effective)
Outcome 3 (QALY)	16.11853	16.11826	0.00027	
Revised Step 3 – Cost per QALY (for epilepsy)				
Costs	\$51,364	\$50,980	\$385	\$825,763
Outcome 3 (QALY)	15.4183	15.4178	0.00047	
Step 3 from original model – Cost per pain-controlled case (for TN)				
Costs	\$16,418.01	\$16,465.61	-\$47.61	\$712.06 (Genotyping less costly and less effective)
Outcome 3 (Pain)	8.7653	8.8322	-0.0669	
Revised Step 3 – Cost per pain-controlled case (for TN)				
Costs	\$14,325	\$14,179	\$147	Dominated
Outcome 3 (Pain)	8.7643	8.8322	-0.0669	

The key drivers of the revised model for epilepsy and the specific results from other one-way sensitivity analyses are presented in Tables 12 and 13 respectively and the tornado diagram for these analyses are presented in Figure 3. Note that the previous key drivers table (Table 8) only tabulated key drivers which did not have unbounded impacts.

Table 12 Key drivers of the model

Description	Method/Value	Impact Base case: HLA-A*31:01 and HLA-B*15:02
Probability of patients treated with CBZ or OXC transitioned from uncontrolled epilepsy to remission	Percentage of 12-month remission of CBZ (254/362) from the SANDA study which was an unblinded RCT in hospital-based outpatient clinics in the UK (Marson et al., 2007).	The variable has such a large effect that the outcome is essentially unbounded within the given range ($\pm 20\%$).
Probability of people who carry at least one of the 2 alleles	Calculated estimate (detailed calculation presented in Section 3A.2.4)	The variable has such a large effect that the outcome is essentially unbounded within the given range ($\pm 20\%$).
Probability of patients treated with VPA transitioned from uncontrolled epilepsy to remission	The HR of remission with VPA compared to CBZ was 0.83, that was $0.7017 \times 0.83 = 0.5824$ (Marson et al., 2007, Plumpton et al., 2015)	The variable has such a large effect that the outcome is essentially unbounded within the given range ($\pm 20\%$).
Utility score of patient who experience uncontrolled epilepsy	Assumed equivalent to the utility score of patients who experience 10+ seizures per year in the usual care group (Gordon et al., 2022).	The variable has such a large effect that the outcome is essentially unbounded within the given range ($\pm 20\%$).
Utility score of patient with remission not experiencing SJS-TEN/DRESS	Assumed equivalent to the utility score of patients with 1–3 seizures in the past year (Gordon et al., 2022).	The variable has such a large effect that the outcome is essentially unbounded within the given range ($\pm 20\%$).
Probability of treatment-induced SJS-TEN/DRESS in non-carriers of HLA-A*31:01 and HLA-B*15:02 alleles	Calculated estimate (detailed calculation presented in Section 3A.2.4)	The variable has such a large effect that the outcome is essentially unbounded within the given range ($\pm 20\%$).
Probability of overall CBZ/OXC-induced SJS-TEN/DRESS	The studies (identified in Section 2) had a range of between 2.3% and 25% of patients having a SCAR reaction. The 2.3% was used in the model aligning with the overall estimate of hypersensitivity reactions highlighted in the PICO (ratified PICO).	The variable has such a large effect that the outcome is essentially unbounded within the given range ($\pm 20\%$).

Abbreviations: CBZ= carbamazepine; DRESS= drug reaction with eosinophilia and systemic symptoms; OXC=oxcarbazepine; PPV= Positive predict value; SJS= Stevens–Johnson syndrome; TEN= toxic epidermal necrolysis.

Table 13 Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case	\$385	0.0005	\$825,763
<i>Probability of patients treated with CBZ or OXC transitioned from uncontrolled epilepsy to remission (base case 0.702; ±20%)</i>			
0.561	\$92	0.0018	\$51,359
0.842	\$585	-0.0004	Dominated
<i>Annual cost of remission treated with CBZ/OXC without SJS-TEN/DRESS (base case \$1,822.87; ±20%)</i>			
\$1,458.30	\$762	0.0005	\$1,635,545
\$2,187.45	\$7	0.0005	\$15,981

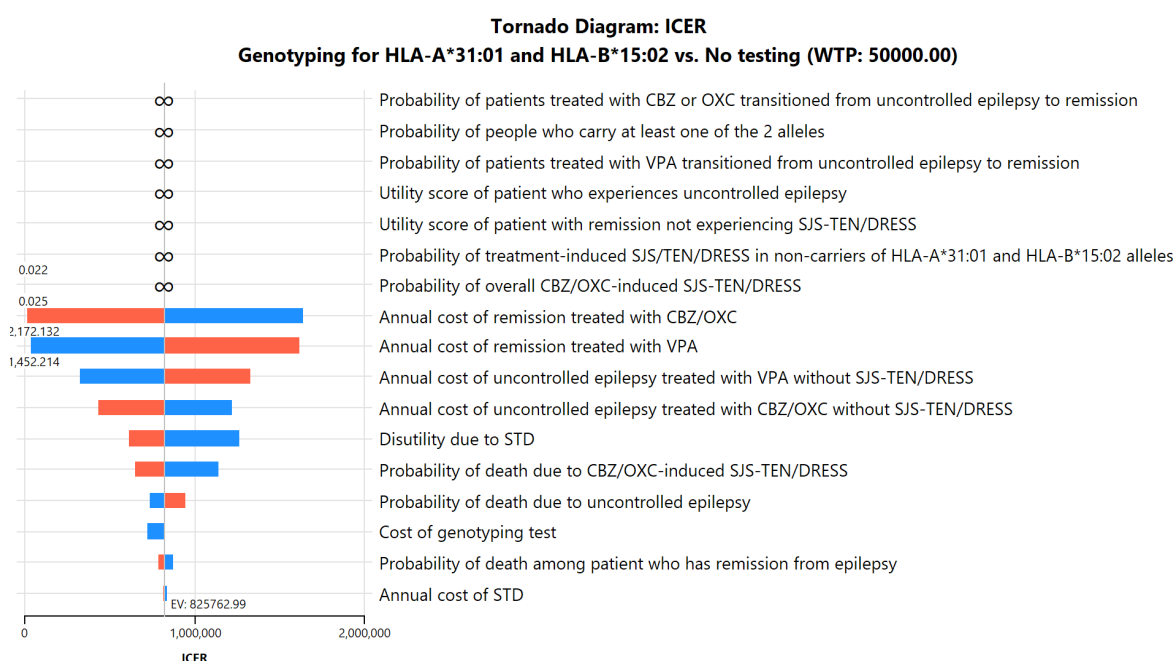


Figure 5: Tornado diagram for one-way sensitivity analysis for epilepsy

For each bar, the blue portion represents the part of the input range from the lower bound to the base case value, while the red portion represents the part of the input range from the base case value to the upper bound. The lack of results for the first seven variables is because the variable has such a large effect that the outcome is essentially unbounded within the given range.

Abbreviations: CBZ=carbamazepine; DRESS=drug reaction with eosinophilia and systemic symptoms; HLA=human leukocyte antigen; ICER=Incremental cost-effectiveness ratio; OXC=oxcarbazepine; SJS=Stevens-Johnson syndrome; TEN= toxic epidermal necrolysis; VPA= Valproate

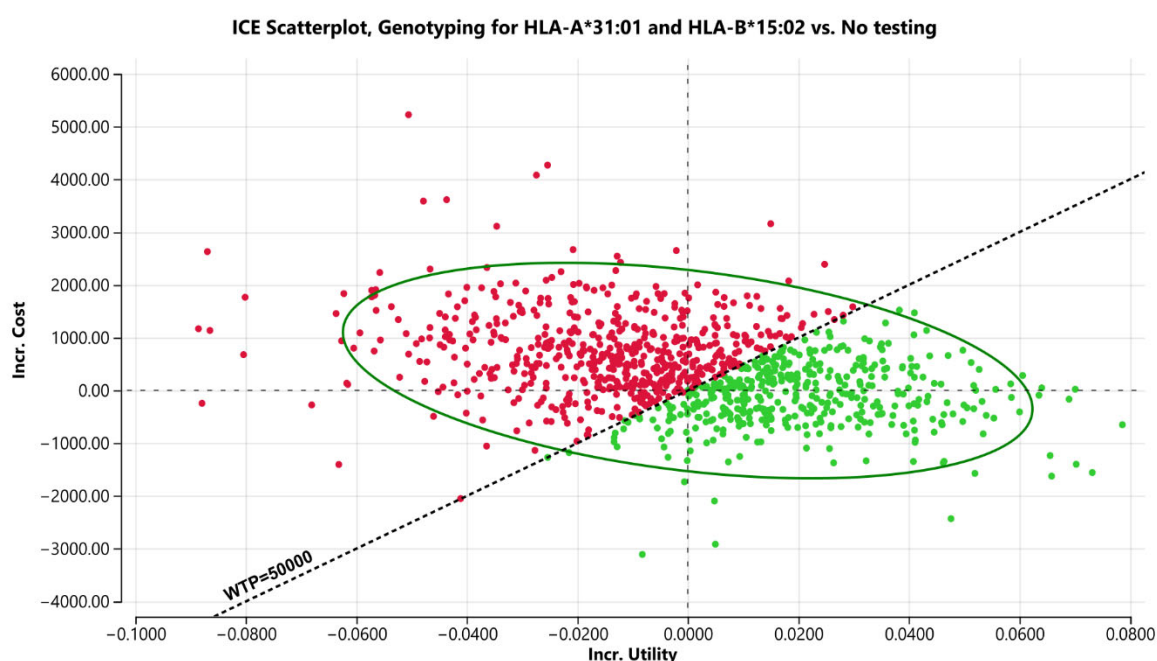


Figure 6: Cost-effectiveness scatter plot for probabilistic sensitivity analysis

14. Financial/budgetary impacts

A market share approach, supported by epidemiological data was used to estimate the financial implications of the introduction of *HLA-A*31:01* and *HLA-B*15:02* genotyping prior to the commencement of carbamazepine or oxcarbazepine. It was assumed that HLA genotyping would only be used for patients that were about to be initiated on CBZ or OXC. While the proposed MBS fee of HLA genotyping (Item AAAA) is \$188, in estimating the financial cost of the item to the MBS it was assumed that 30% of patients would be tested in hospital where a 75% benefit would apply while the remainder would occur out of hospital and the 85% benefit would apply.

Table 14 Data sources and parameter values applied in the utilisation and financial estimates.

Data source	Justification
PBS - R2024-093: Patient counts either for drugs Carbamazepine or Oxcarbazepine by quarter and financial year from 2018-19 to 2022-23.	The epidemiology of epilepsy, trigeminal neuralgia and bipolar, and the proportion of patients receiving either CBZ or OXC is poorly understood. Data on the actual figures of patients receiving CBZ and OXC is more accurate and less open to biases in the estimates of people likely to receive CBZ or OXC in the future.
Requested PBS and RPBS items processed from July 2023 to 2024 Pharmaceutical Benefits Schedule Item Reports (Services Australia, 2024) Proportion: CBZ 87.2%/OXC 12.8%	Proportion of prescriptions dispensed for either CBZ or OXC needed to work out the number of patients prescribed each from the PBS data above.
Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies (Kirsten M. Fiest et al., 2017) Epilepsy (61.44 per 100,000 person-years)	Only prevalence data was available for Australia. This presents the best incidence rate.
The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK (MacDonald et al., 2000)	No data on the prevalence of trigeminal neuralgia is available for Australia. This Paper is the best estimate for a similar population.

Trigeminal neuralgia (6.15 per 100,000 person-years)	
ABS National Study of Mental Health and Wellbeing Bipolar disorder (4 per 100,000 person-years) (Australian Bureau of Statistics, 2020-2022)	This is the best estimate of bipolar disorder in Australia.
Australian Institute of Health and Welfare (2022) – Epilepsy in Australia (Health & Welfare, 2022) Number of people with epilepsy treated with carbamazepine (9.4%) or oxcarbazepine (0.8%)	
Preliminary results from the Australian Genetics of Bipolar Disorder Study: A nation-wide cohort (Lind et al., 2023) Proportion of Bipolar disorder patients receiving CBZ = 10.3%	The Australian Genetics of Bipolar Disorder Study is a nation-wide cohort of adults living with bipolar disorder.
Epidemiology and treatment of neuropathic pain: the UK primary care perspective (Hall et al., 2006) Number of people with trigeminal neuralgia treated with carbamazepine = 58%	Local expert opinion estimates 100%
Census of Population and Housing: Cultural diversity data summary, 2021 (Australian Bureau of Statistics, 2021) and Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. (Phillips et al., 2018)	As no carrier frequency information available for Australia the frequency is based on published data on ancestry and carrier frequency and on Australian ancestry data.
Australian refined diagnosis-related groups (AR-DRG) data cubes Australian refined diagnosis-related groups (AR-DRG) data from the National Hospital Cost Data Collection Report version 11 (Independent Health and Aged Care Pricing Authority, 2023b)	Costs associated with SJS/TEN were based on ARDRG J68A and updated to match length of stay demonstrated in
Published literature on proportion of people with CBZ/OXC hypersensitivity reactions. Shah et al. 2017	The evidence on the proportion of patients with a <i>HLA-B*15:02</i> or <i>HLA-A*31:10</i> genotype that would lead to a hypersensitivity reaction was limited and poor quality. The studies had a range of between 2.3 and 25% of patients having a SCAR reaction. The 2.3% estimate was used as it aligns with the overall estimates of hypersensitivity reactions highlighted in the PICO.

Abbreviations: AR-DRG= Australian refined diagnosis-related groups; CBZ=carbamazepine; DRESS=drug reaction with eosinophilia and systemic symptoms; HLA=human leukocyte antigen; OXC=oxcarbazepine; PBS= Pharmaceutical Benefits Scheme; RPBS= Repatriation Pharmaceutical Benefits Scheme; SJS=Stevens–Johnson syndrome; TEN= toxic epidermal necrolysis; SCAR= severe cutaneous allergic reactions

Table 15 Net financial implications of *HLA-A*31:01* and *HLA-B*15:02* genotyping prior to the commencement of carbamazepine or oxcarbazepine to MBS.

Parameter	2025	2026	2027	2028	2029	2030
Estimated use and cost of the proposed health technology						
Total eligible number of patients	9,506	8,991	8,476	7,960	7,445	6,929
Uptake if reimbursed	50%	60%	70%	80%	90%	100%
Utilisation of AAAA (AxB)	4,753	5,395	5,933	6,368	6,700	6,929
Item AAAA Cost	\$732,753	\$831,632	\$914,631	\$981,691	\$1,032,872	\$1,068,175
Financial implications for the MBS	\$732,753	\$831,632	\$914,631	\$981,691	\$1,032,872	\$1,068,175
Net financial impact to the MBS	\$732,753	\$831,632	\$914,631	\$981,691	\$1,032,872	\$1,068,175

Abbreviations: MBS = Medical Benefits Scheme; HLA=human leukocyte antigen

It was estimated that in the first year of listing the new MBS item would have a net financial implication of \$733,000, rising to \$1.068 million in year 6. This equates to a net six-year financial implication of approximately \$5.6 million.

- The average cost of the proposed technology per patient per once in a lifetime is \$188.
- The average frequency of use of the proposed technology is once per lifetime.

It is expected that the listing of *HLA* genotyping will lead to a change in use of PBS items from CBZ/OXC to Valproate/Gabapentin. It is estimated that *HLA* genotyping will save the PBS between \$22,000 in year one to \$32,000 by year six (Table 16).

Table 16 Net financial implications of *HLA* genotyping to the PBS

	2025	2026	2027	2028	2029	2030
Cost with listing <i>HLA</i>	\$66,796	\$75,810	\$83,376	\$89,489	\$94,155	\$97,373
Cost without listing <i>HLA</i>	\$89,010	\$101,022	\$111,104	\$119,250	\$125,467	\$129,755
Net cost to PBS	-\$22,214	-\$25,212	-\$27,728	-\$29,761	-\$31,313	-\$32,383

Source: Excel workbook "Utilisation and Cost Model_basecase", sheet "3. PBS costs".

Abbreviations: PBS= Pharmaceutical Benefits Scheme

It is expected that the listing of *HLA* genotyping will lead to a reduction in costs to state governments due to a reduction in hospitalisation from CBZ/OXC hypersensitivity reactions.

Table 17 summarises the total cost to state/territory and commonwealth government health budgets. The listing of *HLA* genotyping will lead to a cost to the government health budgets of \$385,000 in year one, rising to \$562,000 by year six. This is a total cost of approximately \$2.9 million over the first six years of listing.

Table 17 Total cost to government health budgets

	2025	2026	2027	2028	2029	2030
Total cost to state governments	-\$325,209	-\$369,093	-\$405,930	-\$435,692	-\$458,407	-\$474,075
Total cost to Commonwealth government	\$710,539	\$806,420	\$886,903	\$951,930	\$1,001,559	\$1,035,792
Net cost to government	\$385,330	\$437,327	\$480,974	\$516,238	\$543,152	\$561,717

Sensitivity analyses were conducted due to some uncertainties and are presented in Table 18 below. Sensitivity analysis demonstrated that the budget impact is most sensitive to the difference in the proportion of *HLA-B*15:02/HLA-A*31:10* patients that develop hypersensitivity reactions, which can change the estimates from cost saving to having a budget impact of costing up to \$4.9 million in year six.

Table 18 Results of sensitivity analyses for net budget impact of making HLA testing available for patients about to commence carbamazepine or oxcarbazepine.

	2025	2026	2027	2028	2029	2030
Base case	\$385,330	\$437,327	\$480,974	\$516,238	\$543,152	\$561,717
HLA genotyping uptake (base case = 20% in 2025 rising to 100% in 2030)						
100% uptake all years	\$770,660	\$728,878	\$687,128	\$645,297	\$603,548	\$561,717
Proportion of trigeminal neuralgia patients treated with CBZ (Base case = 58%)						
100%	\$382,912	\$434,583	\$477,956	\$512,999	\$539,745	\$558,193
Proportion of patients with <i>HLA-B*15:02/HLA-A*31:10</i> with hypersensitivity reaction (Base case 2.3%)						
25%	-\$2,824,342	-\$3,205,461	-\$3,525,377	-\$3,783,853	-\$3,981,127	-\$4,117,198
5%	\$3,563	\$4,044	\$4,447	\$4,773	\$5,022	\$5,194
0.5%	\$639,842	\$726,182	\$798,658	\$857,214	\$901,906	\$932,732
MBS Item fee (base case = \$188)*						
\$182	\$341,633	\$387,461	\$425,930	\$457,010	\$480,732	\$497,095
\$139	\$194,347	\$220,572	\$242,586	\$260,372	\$273,946	\$283,310
\$89.13	-\$28	-\$32	-\$35	-\$37	-\$39	-\$41
MBS Benefit Split (base case = 70% of patients at 85% benefit, remainder at 75% benefit)						
100% at 75% benefit	\$322,778	\$366,334	\$402,895	\$432,435	\$454,980	\$470,531

Source: Excel workbook "Utilisation and Cost Model"

Abbreviations: CBZ=carbamazepine; HLA=human leukocyte antigen; OXC=oxcarbazepine

The clinical uncertainty around the efficacy of *HLA* genotyping and the ability of reduced hypersensitivity reactions has the biggest impact on the financial implications.

15. Other relevant information

Other considerations include:

- Equity related to access: *HLA* genotype testing is not yet widely available; therefore, specimens may need to be sent interregional or interstate. This may have implications for equity of access for those in rural, regional or remote areas. There is also the potential that *HLA* testing may delay treatment commencement; availability and access of the test – particularly for those outside metro areas – which may result in further delays.
- Equity related to First Nations people: There is currently a lack of evidence for all outcomes in First Nations people. As there were no published studies identified which were conducted in any Australian sample. However, there is some data on <http://www.allelefrequencies.net/> that included allele frequencies of *HLA-A*31:01* for First Nations people from Australia Yuendumu Aborigine (2.9%) and the Australia Cape York Peninsula Aborigine (0.5%). Neither population had *HLA-B*15:02* present though there are other First Nations people listed on the database which did have *HLA-B*15:02*. There was no way to determine the exact source of this information,
- Ethical considerations: *HLA* genotyping does not have the same ethical considerations as other types of genetic testing. This test only provides useful information for an individual about their risk of experiencing hypersensitivity reactions. As such, findings with any other clinical utility or meaning are highly unlikely, i.e it won't give information about other conditions. In addition, it provides little information for family or relatives as it is only relevant to patients about to be treated with CBZ/OXC. Cascade testing is not recommended as it won't give any information to the relatives that can be actioned.

16. Key issues from ESC to MSAC

Note: This ESC report includes information regarding the medicines in scope and the economic evaluation provided by the assessment group after the ESC meeting which respond to ESC requests for clarification. Post-ESC information is highlighted in *italics*.

Main issues for MSAC consideration

Clinical issues:

- There are a lack of data for the Australian population, for both First Nations people and the general population. There is higher prevalence of the alleles in people with partial or complete East Asian ancestry, especially for *HLA-B*15:02*. The included studies have a high risk of bias, as they primarily included an East Asian population. The applicability of these studies to the Australian population is uncertain.
- There was no evidence presented to support the claim that alternative treatments are non-inferior in terms of effectiveness if CBZ/OXC are withheld due to predicted adverse drug reactions (either due to a positive genotype test or influenced by any genotyping guideline in the absence of testing).
- There is insufficient information to determine whether it is appropriate to expand the testing under the proposed service to all drugs in the dibenzoazepine class.
- ESC considered it appropriate to revise the item descriptor to allow testing during the initiation of treatment but only in cases of urgent clinical need. However, testing before treatment has started should still be the preferred clinical practice.

Economic issues:

- *The revised ICER for testing of patients with epilepsy was more than \$800,000 per QALY. Pre-treatment HLA genotyping for trigeminal neuralgia was dominated by usual care (where the health outcome reported was in terms of pain controlled cases avoided). However these findings are highly uncertain, reflecting the uncertainty on the clinical evidence.*
- Given the scarcity of evidence, the models relied on many assumptions regarding the utilities and costs which were highly uncertain. In particular, utilities were applied for remission and uncontrolled epilepsy based on quantity of seizures per year, but depending on the types of seizures experienced, seizure quantity does not necessarily equate to severity. Simplifying assumptions were also made about the direct health care costs for people with uncontrolled epilepsy compared to direct health care costs for those with controlled epilepsy.

Financial issues:

- The uptake rate of *HLA* genotyping is unclear. This has a major impact on the MBS budget projections, making the financial impact uncertain. This is problematic if clinical acceptance and use are lower than expected.

ESC discussion

ESC noted this application from the Royal College of Pathologists of Australasia (RCPA) is for Medicare Benefits Schedule (MBS) listing of human leukocyte antigen (*HLA*)-A*31:01 and *HLA*-B*15:02 genotyping to predict carbamazepine- (CBZ-) or oxcarbazepine- (OXC-) related drug hypersensitivity reactions in patients who are about to start CBZ or OXC treatment. This is the first time MSAC has considered this application.

ESC noted that CBZ is an antiepileptic medication commonly used to treat various conditions, including epilepsy, trigeminal neuralgia (TN), mania and bipolar affective disorders. OXC is an antiepileptic medication used as a first-line treatment for epilepsy. Some patients are hypersensitive to these medications due to a variant in their *HLA* gene, which can cause adverse drug reactions. Some of these reactions are severe, including Stevens-Johnson syndrome (SJS), toxic epidermal necrosis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. This proposed testing will potentially identify patients who are at-risk to severe drug reactions before they start treatment with these drugs.

ESC noted the consultation feedback, which comprised seven responses and was largely supportive of the application. Submissions stated that any disadvantages from waiting for the test results before starting treatment were insignificant compared to the benefits of testing. One submission noted that public funding of *HLA* genotyping would ensure alignment with international guidelines and standards. Many organisations noted the higher prevalence of the target *HLA* variants in people of Asian ancestry and stated that this group was especially important to test. The pre-ESC response also referred to this and cited the fact that 17.4% of people in Australia self-reported Asian ancestry in the 2021 Census. However, ESC noted the proven unreliability of people self-identifying their ancestry and therefore considered that the test should be available to all people, regardless of their ancestry.

ESC noted that consultation feedback also raised the issue that the proposed descriptor should not be limited to people with certain medical conditions, but could alternatively specify that the test is for people commencing use of CBZ or OXC, as both CBZ and OXC are used for a variety of indications. ESC noted feedback requesting further clarity around which types of specialists would be able to request the test.

ESC considered that it did not have enough information or evidence to provide advice on whether expanding the proposed testing to all drugs in the dibenzazepine class was appropriate and proposed some additional work that could be undertaken to inform MSAC's consideration of this matter. *Post-ESC, the assessment group provided some further clarification on this issue, noting that PASC (PICO Advisory Subcommittee) had also considered in the PICO for the application whether the proposed genotype testing should be expanded and had noted that such an*

expansion would involve broadening the intervention and population, with testing prior to commencement of treatment for potentially quite a number of drugs (Carbamazepine, Oxcarbazepine, Clomipramine, Clozapine, Imipramine, Mianserin are currently listed on the PBS; Desipramine, Esmirtazapine, Lofepramine, Norclozapine, Opipramol, Setiptiline, Trimipramine are not). This may also require genotyping for more than the two proposed alleles and expanding the list of drugs would also make the required health technology assessment (HTA) considerably more complex.

ESC noted from the pre-ESC response that testing after treatment has started is feasible, as serious drug reactions tend to manifest within 7–15 days and the test turnaround time is 5–7 days. ESC therefore considered it appropriate to revise the item descriptor to allow testing during the initiation of treatment but only in cases of urgent clinical need. ESC considered that testing before treatment has started should still be the preferred clinical practice.

ESC noted the proposed MBS item descriptor. Regarding the fee, ESC considered \$188 may be too high and noted that the suggested reduced fee of \$139 may be sufficient when considering economies of scale. ESC noted that existing items which could be referred to help establish an appropriate fee were MBS item 73320 (\$40.55) for detection of *HLA-B*27* by nucleic acid amplification, MBS item 73317 (\$36.45) for detecting genetic mutations for haemochromatosis and MBS item 71151 (\$118.85) for phenotyping of 2 or more antigens of *HLA-DR*, *HLA-DP* and *HLA-DQ*. In addition, Sonic Genetics lists a *HLA-B*15:02* test at \$80. ESC considered this type of testing would lend itself well to batching, which would reduce laboratory costs. On the other hand, ESC also noted rising input costs since existing MBS items were listed, and the increasing complexity of identification and interpretation of HLA alleles as their numbers increase. ESC noted the pre-ESC response's observation that although from a technological perspective it may be possible to reduce costs by covering both *HLA-A*31:01* and *HLA-B*15:02* in a single test, most laboratories would conduct separate tests, especially as a combined test would need to be developed and validated.

ESC noted the explanatory note, which stated 'genetic testing to be conducted in line with current guidelines and should include at least (but not be limited to) *HLA-B*15:02* and *HLA-A*31:01*'. ESC noted from the pre-ESC response that *HLA-B*15:21* was also identified as an allele of concern for patients commencing treatment with CBZ and OXC and noted that the pre-ESC response observed that this emphasised the importance of the item descriptor not being limited to *HLA-A*31:01* and *HLA-B*15:02*. ESC considered that this note should also include advice about the limitations of test sensitivity and advise that even if a patient tests negative this does not completely rule out the possibility of adverse drug reactions.

ESC noted the current and proposed clinical management algorithms.

ESC noted that Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are available for HLA genotyping and the use of CBZ and OXC. Currently in Australia, the genotyping is available as individual tests, with an associated External Quality Assurance program.

ESC noted that the clinical evidence was derived from two main studies from China (Chang et al. 2023²¹) and Hong Kong (Chen et al. 2014²²). Overall, ESC considered the certainty of evidence to be low to very low for direct test to health outcomes and test accuracy outcomes. ESC noted:

- the high risk of bias (homogenous ancestry)
- that there was direct evidence of *HLA-B*15:02* testing alone

²¹ Chang, B. L., Liu, J. R., Chang, S. H., & See, L. C. (2023). Impact on carbamazepine usage and cutaneous adverse reactions before and after the reimbursement of *HLA-B*1502* genotyping in Taiwan, 2000–2017: A nationwide longitudinal study. *Epilepsia*, 64(10), 2679–2689.

²² Chen, Z., Liew, D., & Kwan, P. (2014). Effects of a *HLA-B*15:02* screening policy on antiepileptic drug use and severe skin reactions. *Neurology*, 83(22), 2077–2084.

- there was no direct evidence for clinical effectiveness of combined *HLA-A*31:01 + HLA-B*15:02* testing and no direct evidence for *HLA-A*31:01* testing alone.

ESC noted the predominantly East Asian population of the studies; one study comprised a Chinese-only population. No Australian studies or resulting estimates of diagnostic yield based on Australian ancestry proportions were included.

ESC noted the clinical claim of noninferior safety. ESC considered the analytical performance of genotyping methods to be robust, as there was a low probability of test-related false positives (FPs) and false negatives (FNs) although specificity was generally higher than sensitivity. ESC also noted that test sensitivity and hence diagnostic yield and prognostic accuracy are highly variable and depend on ancestry, whether the treatment is CBZ or OXC, and the type of adverse reaction that is expected to occur. ESC also noted that not all patients testing positive for the genotypes will be at increased risk of drug hypersensitivity reactions and not all patients testing negative for the genotypes will have no risk of drug hypersensitivity reactions. Clinical management in practice may result in patients identified as having a:

- high risk allele who are not actually at risk of drug hypersensitivity reactions unnecessarily changed to an alternative, possibly less effective, therapy
- negative genotype test result, who are still at risk of drug hypersensitivity reactions, not receiving an alternative treatment. However, these patients may still be at risk of drug hypersensitivity reactions because a negative genotype does not guarantee that a patient is not at risk for adverse reactions because the 2 alleles tested for in the application are not the only alleles associated with causing adverse drug reactions to CBZ and OXC.

ESC noted the clinical claim that *HLA-A*31:01* and *HLA-B*15:02* genotyping before starting CBZ or OXC is superior compared to no pre-treatment genotyping for predicting CBZ- or OXC-related drug hypersensitivity. As noted above, there was no direct evidence for clinical effectiveness of combined *HLA-A*31:01 + HLA-B*15:02* testing, therefore ESC considered there to be insufficient evidence to determine the effectiveness of combined *HLA-A*31:01* and *HLA-B*15:02* genotyping before starting CBZ or OXC compared to no pre-treatment genotyping for:

- improving outcomes of overall survival, morbidity or mortality
- preventing CBZ- or OXC-related drug hypersensitivity (from switching to an alternative treatment).

ESC noted that while there is evidence that implementation of policies for *HLA-B*15:02* genotyping before starting CBZ in East Asian populations reduces CBZ prescription and incidence of severe cutaneous adverse reactions (SCARs), adherence to the policy, that prescribing of CBZ or non-CBZ therapy should only occur after a patient's test result is available, was low (26.4%)². ESC noted that this was evidenced by 40% of patients starting a non-CBZ therapy before the test result became available. Therefore, ESC considered that causality between testing and outcomes could not be ascertained from this study. ESC considered there to be evidence for clinical effectiveness if each allele is assessed separately; however, as noted previously diagnostic yield and prognostic accuracy are highly variable.

ESC also noted data on the prevalence of these variant alleles reported in the CPIC Guidelines (last updated 2017) does not reflect higher prevalence figures reported in more recent studies.²³
24 25

ESC noted that the economic evaluation in the Department-contracted assessment report (DCAR) comprised a decision tree with Markov model which reported the results of a cost effectiveness analysis in terms of cost per patient with severe hypersensitivity reactions avoided and the results of separate cost utility analyses, one for epilepsy and one for TN. ESC noted the following features of the models and related issues:

- The high uncertainty of the available evidence (as previously discussed) carries over into the uncertainty of the cost effectiveness and ICER findings from the economic evaluation.
- The short term CUA model for epilepsy had a time horizon of 3 months while the long term CUA model had a lifetime horizon. The CUA model for TN had a 10 year time horizon. While these time horizons were acceptable, ESC considered that there were problems with the models' structure which employed annual cycles because monthly cycles may be more appropriate as this better aligns with therapy switching that is common in patients with epilepsy and reflects actual clinical practice.
- The models employed some estimates based on Australian data which was appropriate for applicability. However false positives (FPs) and false negatives (FNs) do not have pathways in the model but were 'included in the costs and outcomes as per guidance by Vellekoop (2021)'. Further clarification was requested on how test sensitivity and specificity and therefore FPs and FNs were incorporated into the model. There were also some specific errors due to input variables not being entered correctly into the model which required correction.
- The model used some inputs derived from patients whose condition was considered 'drug resistant' (i.e., they had to have failed at least 2 prior antiseizure medications) that differed from the PICO population which referred to a broader population of patients about to start CBZ or OXC regardless of their epilepsy severity.
- Given the scarcity of evidence, the models relied on many assumptions regarding the utilities and costs which were highly uncertain. In particular, ESC noted that utilities were applied for remission and uncontrolled epilepsy assuming that 10 or more seizures per year 'constituted uncontrolled epilepsy and 1–3 seizures per year constituted 'remission', but seizure quantity does not necessarily equate to severity. Another example was that hospitalisation costs were derived from a sample of 66 patients from real-world data in Queensland and it was assumed that the direct health care costs for people with uncontrolled epilepsy were equivalent to the costs incurred by patients admitted to hospital, while those with controlled epilepsy were not hospitalised.
- Face validity was not discussed in the DCAR and it was not clear if clinicians validated the model decisions; although model traces were performed.

Post-ESC the assessment group clarified that the model incorporated FPs, FNs and the PPV by following the clinical utility of the intervention. i.e. 'false negative' patients follow the test negative arm and are identified in the treatment induced drug hypersensitivity reactions branch of that arm using the PPV from the clinical evidence. Thus, given the disease rate and the carrier rate in the model, the proportion of non-carriers that would develop hypersensitivity reactions

²³ Vakrinou, A., Bellampalli, R., Gulcebi, M. et al. (2023). Risk-conferring HLA variants in an epilepsy cohort: Benefits of multifaceted use of whole genome sequencing in clinical practice. *Journal of Neurology, Neurosurgery and Psychiatry*, 94(11), 887-892.

²⁴ Shah, S. N., Gammal, R. S., Amato, M. G., et al. (2021). Clinical Utility of Pharmacogenomic Data Collected by a Health-System Biobank to Predict and Prevent Adverse Drug Events. *Drug Safety*, 44(5), 601-607. <https://doi.org/10.1007/s40264-021-01050-6>

²⁵ Zhou Y, Krebs K, Milani L, Lauschke VM. Global Frequencies of Clinically Important HLA Alleles and Their Implications For the Cost-Effectiveness of Preemptive Pharmacogenetic Testing. *Clin Pharmacol Ther*. 2021 Jan;109(1):160-174..

was estimated to produce the assumed PPV of 0.77. FPs are not specifically identified in the model, but they follow the clinical utility of the test through the test positive branch of the intervention arm. The assessment group also clarified that drug resistant populations were not used in the model, rather the efficacy data was based on clinical trial patients that had two or more clinically definite unprovoked epileptic seizures in the previous year, which aligns with the PICO population.

ESC noted that the stepped model used valproate (VPA) as an alternative treatment for CBZ/OXC because reactions to this drug appeared to be negligible, but ESC noted that although VPA is a common first drug of choice for epilepsy it is potentially used to manage a different type of seizure compared to the seizures treated with CBZ.²⁶ ESC also noted that VPA was one of the cheaper agents on the PBS and newer agents (topiramate and levetiracetam) were significantly more expensive. This model resulted in a base case incremental cost-effectiveness ratio (ICER) of \$3,337 per patient with positive genotyping results which was within the range of other MSAC supported genotyping germline tests. However, ESC noted that this equated to \$428,125 per patient with severe drug hypersensitivity reactions avoided.

Separate CUAs were reported (i.e. with separate costs per QALY) for epilepsy and TN. The DCAR reported that testing was found to be dominant for patients with epilepsy. However, ESC disputed the interpretation of the base case results for epilepsy because the incremental gain in QALY was negligible and therefore testing should be considered equivalent compared to no testing rather than dominant. ESC noted that the pre-ESC response clarified that usage of CBZ for TN patients in the economic model should be 100% instead of 12.78% and that correcting this error switched the ICER for testing of TN patients from 'less costly and less effective' to dominated. *Post-ESC correction of errors in the economic evaluation switched the ICER for patients with epilepsy from 'dominant' to more than \$800,000 per QALY.*

ESC noted that the financial impact to the MBS in years 1–6 was approximately \$5.6 million (with a test fee of \$188) and \$4.1 million (with a test fee of \$139) based on an uptake of about approximately 9,500 patients per year, which would decrease after year 1. However, this uptake is highly uncertain. The average frequency of use of the proposed technology is once per lifetime. The *HLA* genotyping was predicted to save the Pharmaceutical Benefits Scheme (PBS) between \$22,000 in year 1 and \$32,000 in year 6 due to a change in use of PBS items from CBZ/OXC to valproate/gabapentin. There would also be some savings in hospitalisation costs associated with adverse drug reactions accruing to State and Territory governments.

ESC noted that the DCAR did not specifically address how First Nations people would be tested under this proposal. This was of concern because First Nations people had higher rates of epilepsy compared to the general population but were also more likely to live in rural and remote areas meaning that these populations were more likely to require testing specimens to be sent interstate or to a regional centre which may delay commencement of treatment. It was also noted that notwithstanding the limited knowledge of the effectiveness of the test among First Nations people (as discussed below), some First Nations people with reduced access to testing may include those of partial ancestry from East Asian and other groups with a high prevalence of the high-risk alleles.

ESC noted that there is no or limited evidence of effectiveness of *HLA* genotyping in First Nations people or the general multi-ancestral population because there are no Australian clinical effectiveness data available. ESC recommended that MSAC give consideration to a proposal to collect (subject to patient consent) ancestry data in test referral forms and/or in data dictionaries in research conducted in Australia to establish and broaden known pathogenic *HLA* alleles in the Australian population. ESC also considered that it was necessary for the applicant to consider how it could work with First Nations communities to address the equity and access issues (as previously noted) associated with providing testing to these communities. More generally, given

²⁶ Marsen et al. (2000). [Carbamazepine versus valproate monotherapy for epilepsy](#). *Cochrane Database of Systematic Reviews*.

the issues identified with testing of HLA alleles, ESC considered that a registry for pharmacogenomics would be helpful, notwithstanding the fact that self-reporting ancestry is proven to be very unreliable. ESC noted that the establishment of a registry would facilitate the linking of clinical data to HLA variant allele data which would also facilitate the production of more direct evidence over time to support the prediction of adverse reaction in various ancestries. Studies using genomic sequencing may infer ancestry and should be considered (within ethically responsible boundaries/conditions) in future research. In addition, ESC considered that the limitations of allele testing should be clearly articulated in associated fact sheets and discussed with patients. ESC noted that pharmacogenomic testing in Australia has lagged behind other high-income countries in terms of general uptake and implementation. ESC considered that continued/expanded education and acceptance of the validity of personalising care for patients based on pharmacogenomics is needed to raise awareness and to support appropriate testing in relevant situations.

ESC noted potential legal issues associated with such testing because if a test is available for *HLA* genotyping and it is not offered or accessible and a severe adverse drug reaction occurs in an individual who would have tested positive to the testing, the litigation risk is moderate to high.

ESC considered there to be a minimal risk of ethical issues arising from this type of genetic testing, as the risk of psychological harm is low if a variant allele is present and is only relevant to that individual. ESC also noted psychological benefits of testing, as knowledge of an allele associated with a risk of adverse reactions provides greater perceived control of choices and health outcomes, potentially lowers the risk of adverse events, and thus avoids psychological and economic burden on carers and family.

Before MSAC considers this application, ESC considered that the following matters which were not addressed in the post-ESC information provided by the assessment group may need to be resolved:

- review any evidence supporting the pre-ESC response's claim that alternative drugs are non-inferior in effectiveness to CBZ and OXC
- confirm whether the choice of VPA in the economic model is an appropriate alternative treatment (or proxy) to CBZ or OXC in relation to epileptic seizure types

ESC advised that the applicant may wish to advise in its response which other drugs (a) fall into the dibenzazepine class (b) are PBS listed, and c) are used for the neurological indications, as this advice would enable MSAC to determine if it is appropriate to expand the testing under the proposed service to all drugs in the dibenzazepine class.

17. Applicant comments on MSAC's Public Summary Document

The College's Working Party would like to express their delight in MSAC approving public funding for HLA genotyping, and would like to take this opportunity to thank the Department for its assistance throughout the assessment process. We remain committed to assisting the Department with the review of utilisation in future, as needed.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)