MSAC Application 1769

Human leukocyte antigen (HLA) testing for hypersensitivity to carbamazepine and oxcarbazepine

Applicant: The Royal College of Pathologists of Australasia

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1   PICO for *HLA-A*31:01* and *HLA-B*15:02* genotyping in patients about to commence treatment with carbamazepine or oxcarbazepine: PICO Set 1

Component	Description
Population	Patients who are about to commence carbamazepine or oxcarbazepine treatment for the first time.
Prior tests	No prior test(s).
Intervention	Genotyping prior to or at commencement of carbamazepine or oxcarbazepine treatment to identify *HLA-A* and *HLA-B* alleles (*HLA-A*31:01* and *HLA-B*15:02*), to identify patients at risk of developing severe drug hypersensitivity reactions (such as SJS, TEN, DRESS or MPE)
Comparator/s	No genotyping prior to or at commencement of carbamazepine or oxcarbazepine treatment.
Reference standard	Clinical utility standard: Ability to predict hypersensitivity to carbamazepine or oxcarbazepine.
Outcomes	Safety outcomes: • Adverse events (AEs) related to *HLA-A*31:01* and *HLA-B*15:02* genotyping. • AEs (or avoided AEs) from any change in patient management, e.g., treatment modifications, monitoring, any differential potential harms by timing of genotyping (i.e., prior to versus at commencement of carbamazepine or oxcarbazepine treatment if applicable). Test performance: • Prognostic accuracy: sensitivity, specificity, positive predictive value, and negative predictive value of *HLA-A*31:01* and *HLA-B*15:02* genotyping to predict severe drug hypersensitivity reactions to carbamazepine or oxcarbazepine (e.g., SJS, TEN, DRESS or MPE). • Any differences in prognostic accuracy by patient characteristics (e.g., age, sex, ancestry) and underlying condition (e.g., epilepsy, trigeminal neuralgia, bipolar disorder). Change in management: • Change in patient management (e.g., modification of therapy, monitoring).

Component	Description
	• Any differences in patient management by patient characteristics (e.g., age, sex, ancestry) and underlying condition (e.g., epilepsy, trigeminal neuralgia, bipolar disorder).

Clinical effectiveness outcomes:

• Direct: Change in patient-relevant health outcomes (e.g. event rates of SJS, TEN, DRESS or MPE, mortality, morbidity of underlying condition, quality of life) comparing patients who received *HLA-A*31:01* and *HLA-B*15:02* genotyping prior to or at commencement of carbamazepine or oxcarbazepine treatment versus those who did not receive *HLA-A*31:01* and *HLA-B*15:02* genotyping prior to or at commencement of treatment.
• Indirect: Change in patient-relevant health outcomes (e.g., mortality, morbidity of underlying condition, quality of life) in patients who experienced carbamazepine or oxcarbazepine related drug reactions severe drug hypersensitivity reactions.
• Any harm from *HLA-A*31:01* and *HLA-B*15:02* genotyping, e.g., false negatives; test turn-around time (TAT) resulting in potential delay in commencing treatment in patients who receive pre-treatment testing, or potential delay in stopping treatment in patients who receive concurrent testing and treatment; false positives leading to unnecessary changes in patient management and potentially less effective therapy.
• Any differential clinical effectiveness outcomes by patient characteristics (e.g., age, sex, ancestry), and underlying condition (e.g., type, stage).
• Any differential clinical effectiveness outcomes by timing of genotyping (prior to versus at commencement of treatment).

Cost-effectiveness outcomes:

• Cost per patient with positive genotyping result (i.e. *HLA-A*31:01* and/or *HLA-B*15:02* variant identified).
• Cost per patient regarding severe drug hypersensitivity reactions avoided.
• Incremental cost per quality-adjusted life year (QALY) gained.
• Any differential results by patient characteristics (e.g., age, sex, ancestry).
• Any differential cost effectiveness results by timing of genotyping (prior to versus at commencement of treatment).

Health system resources:

• Cost of *HLA-A*31:01* and *HLA-B*15:02* genotyping and associated service costs if applicable.
• Change in the costs associated with the investigation, monitoring, and management of severe drug hypersensitivity reactions (e.g., drugs, hospitalisation).
• Change in the cost of treatment because of a change in clinical management (e.g., alternative non-carbamazepine or oxcarbazepine-based treatment).
• Any differential impact on resource use and costs by timing of genotyping (prior to versus at commencement of treatment).
• Total Australian Government healthcare costs. |

Component	Description
Assessment questions	What is the comparative safety, effectiveness, and cost-effectiveness of genotyping (pre-treatment or at treatment commencement) to identify *HLA-A* and *HLA-B* alleles (*HLA-A*31:01* and *HLA-B*15:02)* versus no genotyping (pre-treatment or at treatment commencement) in patients about to commence carbamazepine or oxcarbazepine treatment?

AE = adverse event; DRESS = drug reaction with eosinophilia and systemic symptoms; HLA = human leukocyte antigen; MPE = maculopapular exanthema; SJS = Stevens–Johnson syndrome; TAT = turnaround time; TEN = toxic epidermal necrolysis

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of *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 was received from the Royal College of Pathologists of Australasia (RCPA) by the Department of Health and Aged Care.

The clinical claim is that the use of pre-treatment *HLA-A*31:01* and *HLA-B*15:02* genotyping in patients who are about to commence carbamazepine or oxcarbazepine treatment results in superior health outcomes compared to no pre-treatment genotyping (p16 of the application).

PICO criteria

Population

The proposed target population for this application is all patients about to commence carbamazepine or oxcarbazepine treatment.

The HLA genes encode major histocompatibility complex (MHC) proteins, which have a significant role in immune defence and differentiating between self and non-self. The HLA-A protein is one of three major class I MHCs and is comprised of the heavier α chain encoded by the *HLA-A* gene and the invariant β_2 microglobulin encoded by the *B2M* gene. The *HLA-A* gene is one of the fastest evolving genes, with thousands of known alleles. The *HLA-B* gene encodes the HLA-B class I MHC, and it too has hundreds of described alleles. HLA alleles are assigned a name by the World Health Organization Naming Committee for Factors of the HLA System. HLA genotyping and phenotyping are also used in matching transplant donors, and detection of one HLA genotype is already MBS-listed (MBS item 73320 for detection of *HLA-B27*, fee $40.55).

The application focused on epilepsy, but it was confirmed during the pre-PASC meeting with the applicant, that all patients about to commence carbamazepine or oxcarbazepine treatment should be included regardless of diagnosis/indication.

Carbamazepine (CBZ) was first discovered and synthesised by Swiss chemist Walter Schindler in 1953, and was initially developed to treat trigeminal neuralgia (Schwarz et al., 2021). In the early 1960s, carbamazepine's anticonvulsant properties were observed in animal experiments and later confirmed in human clinical studies. Carbamazepine's mechanism of action remains incompletely understood, but it is believed that its diverse therapeutic effects do not arise from a single mechanism. Researchers have suggested that carbamazepine maintains sodium channels in an inactivated state. By doing so, it reduces the number of channels available for activation, ultimately inhibiting the generation of action potentials (Maan et al., 2023). In addition as with other anticonvulsants, carbamazepine is suggested to bind to the alpha subunit of Voltage-Gated Sodium Channels (VGSC). Specifically, it targets a binding pocket formed by the external pore loop and the pore-lining part of domain IV (Maan et al., 2023; Schwarz et al., 2021).

Carbamazepine, an anticonvulsant medication, is commonly used as a first-line treatment for various conditions. Carbamazepine is indicated for (according to product information (PI)):

1. Epilepsy

   - Complex or simple partial seizures (with or without loss of consciousness) with or without secondary generalised seizures

   - Generalised tonic-clonic seizures

   - Mixed seizure patterns incorporating the above.

2. Trigeminal neuralgia

   - For relief of pain in idiopathic trigeminal neuralgia and trigeminal neuralgia due to multiple sclerosis; and in idiopathic glossopharyngeal neuralgia.

3. Mania and bipolar affective disorders

   - Treatment of mania and maintenance treatment of bipolar affective disorders to prevent or attenuate recurrence.

While it is available under several brand names, only Tegretol® (Novartis Pharmaceuticals Australia Pty Ltd) and Carbamazepine Sandoz (Sandoz Pty Ltd) are listed on the Pharmaceutical Benefits Scheme (PBS). Carbamazepine is suitable for monotherapy and combination therapy in epilepsy and is usually not effective in absence seizures, atonic seizures and myoclonic seizures and should not be used for status epilepticus.

The PIs for Tegretol and Carbamazepine Sandoz have special warnings for serious dermatological reactions:

"Serious dermatological reactions, including toxic epidermal necrolysis (TEN; also known as Lyell's syndrome) and Stevens-Johnson syndrome (SJS), have been reported very rarely with carbamazepine. Patients with serious dermatological reactions may require hospitalisation, as these conditions may be life-threatening and may be fatal. Most of the SJS/TEN cases appear in the first few months of treatment with carbamazepine. If signs and symptoms suggestive of severe skin reactions (e.g. SJS, Lyell's syndrome/ TEN) appear, Carbamazepine Sandoz should be withdrawn at once and alternative therapy should be considered."

Oxcarbazepine, a compound initially synthesised in 1966, is a keto variant of carbamazepine distinguished by an additional oxygen atom on the dibenzazepine ring (Shorvon, 2009). This structural modification circumvents the epoxidation phase in metabolism, thereby diminishing interaction risks. It also presents a significantly reduced likelihood of bone marrow suppression and liver dysfunction. Functionally akin to carbamazepine, it operates by blocking neuronal sodium channels, yielding clinical outcomes comparable to its counterpart. By 1989, oxcarbazepine's primary attributes relative to carbamazepine were established in a clinical trial; equivalent effectiveness, improved tolerability, reduced interaction and allergy risks, but a higher rate of hyponatremia (Dam et al., 1989). Oxcarbazepine-induced cutaneous adverse drug reactions (ADRs) presented with less clinical severity including limited skin detachment (all ≦ 5%) and no mortality compared to carbamazepine. Despite its subsequent use, oxcarbazepine ranked 11th (0.8%) of

prescriptions dispensed for antiepileptic medications in 2019-2020 in Australia, compared with carbamazepine which ranked 5th (9.4%) (Figure 4.1, AIHW 2022).

Oxcarbazepine is an anticonvulsant medication used as a first-line treatment for epilepsy. Oxcarbazepine is indicated for use "as monotherapy or adjunctive therapy for the treatment of partial seizures and generalised tonic-clonic seizures, in adults and children" (TGA-approved Product Information (PI) for oxcarbazepine (Trileptal®), June 2020). Oxcarbazepine is marketed as Trileptal by Novartis Pharmaceuticals Australia Pty Limited and is listed on the PBS. The PI for Trileptal has a special warning for life threatening dermatological reactions:

"Serious dermatological reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (Lyell's syndrome) and erythema multiforme, have been reported very rarely in association with the use of Trileptal. Patients with serious dermatological reactions may require hospitalisation, as these conditions may be life-threatening and very rarely be fatal. Trileptal associated cases occurred in both children and adults. The median time to onset was 19 days. Several isolated cases of recurrence of the serious skin reaction when rechallenged with Trileptal were reported. Should a patient develop a skin reaction with Trileptal, consideration should be given to discontinuing Trileptal and prescribing another anti-epileptic medication."

PASC noted the proposed population was patients about to commence carbamazepine or oxcarbazepine treatment, and considered whether the proposed genotype testing should be expanded to include patients about to commence treatment with other drugs in the same drug class of dibenzoazepines or even all aromatic anticonvulsants (accounting for about 40% of anticonvulsant prescriptions). PASC noted that such an expansion would involve broadening the intervention and population, with testing prior to commencement of treatment for potentially quite a few drugs, and possibly genotyping at more than the two proposed single nucleotide polymorphisms (SNPs). PASC considered that while there may be clinical utility in also providing genotyping before prescribing drugs other than carbamazepine and oxcarbazepine, eslicarbazepine was not available on the PBS, and expanding the list of drugs would also make the required health technology assessment (HTA) considerably more complex. At present PASC advised that the population should be patients about to commence either of the proposed two drugs (carbamazepine and oxcarbazepine), without restriction by indication.

Treatment population

The treatment population is intended to consist of all patients about to commence carbamazepine and oxcarbazepine treatment. Current indications for carbamazepine and oxcarbazepine include epilepsy, trigeminal neuralgia, and bipolar disorder, which are discussed below.

Epilepsy

Epilepsy is the most common indication for prescribing carbamazepine and is the only current indication for oxcarbazepine. Epilepsy is a neurological condition characterised by unprovoked, recurrent seizures. These seizures result from sudden abnormal electrical activity in the brain. Seizures do not always involve convulsions but can include changes to sensation, awareness, behaviour, or movement. Epilepsy can be caused by numerous factors including; injury and stroke, prolonged oxygen deprivation, brain infections and tumours, neurodegenerative conditions (such as dementia), genetic attributes, and congenital abnormalities, with just under half having unknown aetiology (Symonds et al., 2021; Thijs et al., 2019).

Approximately 1 in every 150 people (0.6%) in Australia currently live with epilepsy. The prevalence is similar for males and females, but is higher in indigenous Australians (1.2%) (Australian Institute of Health and Welfare, 2022). There are no published incidence rates for Australia but based on a systematic review of international studies, the mean pooled estimate for epilepsy incidence is 61.44 per 100,000 person-years (95% CI 50.75–74.38). However the individual country estimates ranged from 33.6 to 215.0 per 100,000 person-years (Fiest et al., 2017). This would put the annual incidence of epilepsy in Australia at an estimated 16,000 per year.

Commonly available anti-epileptic drugs such as valproate, levetiracetam, lamotrigine, carbamazepine, oxcarbazepine and gabapentin (Manford, 2017), are capable of controlling seizures with about a 5% annual remission rate (Manford, 2017). Carbamazepine was the 5th most commonly prescribed, accounting for 9.4% of anti-epileptic drug prescriptions in Australia in the year 2019-20 with oxcarbazepine being the 11th most commonly prescribed medication for epilepsy (Australian Institute of Health and Welfare, 2022). Carbamazepine is prescribed specifically for partial seizures with complex symptomatology (psychomotor, temporal lobe), generalised tonic seizures (grand mal), and mixed seizure patterns.

Trigeminal neuralgia

Trigeminal neuralgia, also known as tic douloureux, is a condition that causes intense pain similar to an electric shock on one side of the face along any of the three divisions of the trigeminal nerve, affecting the lips, eyes, nose, scalp, forehead, upper jaw, and lower jaw, mouth, gums and teeth (Zakrzewska & Linskey, 2009). Attacks of pain can be triggered by everyday activities such as brushing the teeth, shaving, applying makeup, or even a light breeze. Patients may experience higher rates of depression, anxiety, and sleep disorders (Zakrzewska & Linskey, 2009).

Trigeminal neuralgia is a rare condition, with no evidence on its incidence or prevalence in Australia. A systematic review reported a prevalence of 0.03 to 3% with women being mostly affected and the affected age range was 37 to 67 years old (De Toledo et al., 2016). Three studies reported an annual incidence of 4.3 to 8 per 100,000 person-years (Katusic et al., 1991; MacDonald et al., 2000; Zakrzewska & Linskey, 2009). Based on the current Australian population this would translate to incident trigeminal neuralgia cases per year ranging from 1,140 to 2,120.

Trigeminal neuralgia is usually treated initially with carbamazepine, often effective for long periods (Allam et al., 2023; Giorgio et al., 2021). If carbamazepine is ineffective or has adverse effects, other anti-seizure medications such as valproate and gabapentin may be used. Other methods of treatment include: cranial nerve block; botulinum toxin injection between the epidermis and the dermis at trigger points where pain is experienced or along the path of the nerve branches involved; neuroablative treatments may be considered, among other treatments that are available (Allam et al., 2023). In the modern era microvascular decompression of an artery or vein impinging upon the proximal trigeminal nerve close to the brainstem is frequently used (Herta et al., 2021).

Bipolar disorder

Bipolar disorder, also known as manic-depressive disorder, is a chronic mood disorder characterised by intense shifts in mood, energy levels, and behaviour. Symptoms include manic and depressive episodes. During manic phases, individuals may experience elevated mood (feeling very happy or irritable) inflated self-esteem or grandiose ideas, increased energy, creativity, and reduced need for sleep, impulsivity or

risky behaviours, unrealistic plans, delusions, or hallucinations (Grande et al., 2016). During depressive episodes individuals may experience low mood and lack of motivation, loss of interest in usual activities, changes in sleep patterns, difficulty concentrating, withdrawal from social interactions and feelings of worthlessness or guilt, sometimes accompanied by suicidal thoughts. There are three types of bipolar disorder: 1) Bipolar I - characterised by severe manic episodes; 2) Bipolar II - involves hypomanic episodes (less severe than mania) and depressive episodes; 3) Cyclothymic Disorder - a milder form with chronic mood fluctuations (Grande et al., 2016).

The incidence of bipolar disease is largely unknown in Australia although estimated at about 2% of the population (Australian Bureau of Statistics, 2023). The age of onset has a wide range but the mean age is approximately 30 years of age, with Bipolar I having an earlier onset than Bipolar II (Baldessarini et al., 2010). Using an average life expectancy of 83 years, this would put the annual incidence of bipolar disease at approximately 4 per 100,000 person years or approximately 10,000 incident cases per year.

Medical treatment of bipolar disease in Australia includes lithium, anti-convulsants (Valproate, Lamotrigine), first-generation antipsychotics (acute treatment of mania; Chlorpromazine, Haloperidol) and second generation antipsychotics (Asenapine, Olanzapine, and Quetiapine) (Malhi et al., 2021; The Royal Australian College of General Practitioner, 2013). Carbamazepine is also commonly used for manic episode control as it can effectively stabilise mood and helps reduce irritability, impulsivity, and hyperactivity associated with mania (Cipriani et al., 2011). Carbamazepine also helps prevent mood swings and contributes to maintaining a more balanced emotional state due to its mood stabilising qualities (Stoner et al., 2007). However, antipsychotic medications surpass traditional mood stabilisers such as lithium, valproate, and carbamazepine in more effectively treating acute manic episodes (Cipriani et al., 2011) which may thus lessen carbamazepine use in this population. In addition, carbamazepine is not listed on the PBS for bipolar disorder, likely reducing its use in bipolar disease and making it difficult to estimate the volume of carbamazepine being used in Australia due to limited data on private prescribing.

Drug hypersensitivity reactions

Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome and maculopapular exanthema (MPE) are drug reactions that are caused by carbamazepine or oxcarbazepine (as well as other drugs including other anticonvulsants) (Hama et al., 2022). SJS and TEN are examples of severe and potentially life-threatening type IV delayed allergic reactions that result from the inappropriate activation of T-cells in response to carbamazepine (Böhm et al., 2018). SJS and TEN are thought to be variants of the same condition with similar clinical features but differentiated by the extent of the body surface area affected: 1–10% for SJS, 10–30% for SJS/TEN overlap and >30% for TEN (Copaescu & Trublano, 2022; Frantz et al., 2021; Owen & Jones, 2021). SJS and TEN are associated with significant morbidity with clinical manifestations including dark-purple skin infiltration, facial swelling, blisters and erosions occupying large areas of the skin, mainly on the trunk and face, mucosal involvement, adenopathy, fever above 38.5°C as well as haematological and biochemical laboratory abnormalities including eosinophilia and elevated liver enzymes (Böhm et al., 2018; Copaescu & Trublano, 2022). DRESS is a severe hypersensitivity reaction characterised by potentially life-threatening generalised cutaneous eruptions with systemic manifestations including maculopapular rash, erythroderma, facial or extremity oedema, purpura, pustules, focal monopolar, mucous-membrane involvement as well as fever above 38.5°C. DRESS may also affect the liver, kidneys and lungs leading to hepatic or renal failure in some cases. MPE, however, is a milder reaction with only the presence of rash

without mucosal or organ involvement, or systemic features (Duong et al., 2017; Phillips et al., 2018). The presence of any of these symptoms warrants immediate cessation of treatment with carbamazepine (as well as drugs in the same family) and urgent hospital referral (Böhm et al., 2018).

Severe drug hypersensitivity reactions to carbamazepine or oxcarbazepine are associated with specific HLA alleles: *HLA-A*31:01* and *HLA-B*15:02*. A meta-analysis reported that the *HLA-A*31:01* and *HLA-B*15:02* alleles are significantly associated with the risk of developing carbamazepine-induced SJS or TEN (OR: 2.88 and OR: 24.51, respectively) (Rashid et al., 2022). The prevalence of these alleles is dependent on the patient's ethnic origin: 10–15% in Han Chinese, Thais, and South-East Asians, <1% in Koreans and Japanese and <0.1% in those with European ancestry (Böhm et al., 2018; Copaescu & Trublano, 2022). However, as either heterozygous carriers or individuals homozygous for either the *HLA-A*31:01* or *HLA-B*15:02* alleles are at risk of a severe cutaneous reaction to carbamazepine, genotyping is recommended for all individuals about to commence treatment with carbamazepine or oxcarbazepine regardless of their apparent ancestry (Pirmohamed, 2023).

The incidence of DRESS syndrome in new users of carbamazepine is estimated to be one per 1,000 to one per 10,000. Although the incidence of SJS and TEN is extremely rare in comparison, estimated to be two per one million people, these reactions are all associated with significant morbidity and mortality, especially as the extent of disease progresses (Duong et al., 2017). SJS has a better prognosis with the rate of mortality in these patients estimated to be 5%. This rate increases sharply to 30% for those patients in the SJS/TEN overlap, then up to 50% for those patients with TEN. The primary cause of mortality is multi-organ failure from sepsis, often from skin or peripheral line infection as well as hypovolaemia from fluid loss (Owen & Jones, 2021). The rate of mortality from DRESS ranges from 1-10%, usually from multi-organ failure, with surviving patients susceptible to autoimmune diseases such as lupus, thyroiditis, diabetes and scleroderma (Duong et al., 2017).

No data are available on the rate of SJS, TEN or DRESS in Australia.

Number of eligible patients

The application form estimated the number of eligible patients for *HLA-A*31:01* and *HLA-B*15:02* genotyping under the proposed MBS listing based on the total number of people with diagnoses of epilepsy and trigeminal neuralgia and the applicant stated that the expected proportion of patients receiving carbamazepine would be 10% in the epilepsy population and 100% of trigeminal neuralgia patients. However, a study in the UK estimated that carbamazepine was used in about 58% of patients (Hall et al., 2006). Utilisation of *HLA-A*31:01* and *HLA-B*15:02* genotyping will be based on the number of people receiving carbamazepine in Australia. Direct sources to collect this information in Australian do not exist so international sources may be utilised for estimation of usage. While there are publicly available PBS usage data for carbamazepine, it is based on prescription data rather than on incidence of new patients. The prescription data for carbamazepine puts it as the 5th most commonly prescribed epilepsy therapy accounting for 9.4% (292,216) of anti-epileptic drug prescriptions in Australia in the year 2019-20 (AIHW 2022). Using 9.4% as an estimate of the proportion of new patients is problematic as it does not take into account treatment durations and changes in the market with new drugs being introduced. However, with such a paucity of data this provides the best local estimate. It is likely that carbamazepine would be used in the majority of patients with trigeminal neuralgia with a UK study demonstrating that 58% of patients received the drug as an initial treatment (Hall et al., 2006). In bipolar disorder, second

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generation anti-psychotic and lithium-based medications are initial choices with carbamazepine being an alternative selection. There is no reliable estimate as to how many patients would receive carbamazepine for bipolar disorder so the same estimate as for epilepsy was used. Availability of relevant data would be further investigated, and selection of estimates justified in the assessment report.

Table 2 presents the estimated number of patients eligible for *HLA-A*31:01* and *HLA-B*15:02* genotyping in the first year of the proposed MBS listing — approximately 2,780 patients— based on the assumptions described in the application and during the PICO development stage.

Table 2 Projected incidence of conditions treated with carbamazepine and the eligible population for *HLA-A*31:01* and *HLA-B*15:02* genotyping, over the first six years of the proposed MBS listing

	2025	2026	2027	2028	2029	2030
ABS population projections (low series) (Australian Bureau of Statistics, 2023)[a]	27,235,315	27,580,551	27,902,964	28,204,391	28,488,756	28,754,774
Epilepsy (61.44 per 100,000 person-years) [b]	16,733	16,945	17,144	17,329	17,503	17,667
Number of people with epilepsy treated with carbamazepine (9.4%) or oxcarbazepine (0.8%)[c]	1,707	1,728	1,749	1,768	1,785	1,802
Trigeminal neuralgia (6.15 per 100,000 person-years) [d]	1,675	1,696	1,716	1,735	1,752	1,768
Number of people with trigeminal neuralgia treated with carbamazepine (58%)[e]	972	984	995	1,006	1,016	1,025
Bipolar disorder (4 per 100,000 person-years) [f]	1,089	1,103	1,116	1,128	1,140	1,150
Number of people with bipolar disorder treated with carbamazepine (9.4%)	102	104	105	106	107	108
Total eligible population	2,780	2,816	2,849	2,880	2,908	2,935

Source: *Table compiled during PICO development based on data from [a] (Australian Bureau of Statistics, 2023); [b] (Fiest et al., 2017); [c]* (Australian Institute of Health and Welfare, 2022); [d] (Katusic et al., 1991; MacDonald et al., 2000; Zakrzewska & Linskey, 2009); [e] (Hall et al., 2006);[f] (Australian Bureau of, 2023).
ABS = Australian Bureau of Statistics; MBS = Medicare Benefits Scheme

PASC noted that in clinical practice, carbamazepine and oxcarbazepine may be considered as potential treatment options for any patients with the TGA-approved indications. These patients would therefore be able to access the proposed genotyping, independent of whether the clinician's final decision was to prescribe carbamazepine/oxcarbazepine or not. Thus the proposed genotyping may potentially become a standard test in all patients who could potentially receive these drugs. PASC therefore considered that the estimated number of patients genotyped may be closer to the total patient populations for all of the relevant clinical indications, rather than the number of unique patients who are about to have carbamazepine or oxcarbazepine for the first time.

Intervention

The intervention proposed is targeted genotyping of all individuals about to commence treatment with carbamazepine or oxcarbazepine to identify *HLA-A* and *HLA-B* alleles (*HLA-A*31:01* and *HLA-B*15:02*). The goal of pre-treatment *HLA-A*31:01* and *HLA-B*15:02* genotyping is to reduce the risk of patients developing SJS, TEN, DRESS or MPE, by identifying patients at risk of these conditions by avoiding treatment with carbamazepine or oxcarbazepine. Genotyping results are considered "positive" if one or two copies of the variant allele are present, that is, being heterozygous or homozygous for either the *HLA-A*31:01* or *HLA-B*15:02* alleles (Pirmohamed, 2023). It was proposed that all patients who are about to commence treatment with carbamazepine or oxcarbazepine should undergo *HLA-A*31:01* and *HLA-B*15:02* genotyping prior to commencing therapy. Individuals who have no variant detected are assumed to have two copies of the normal HLA alleles and can commence carbamazepine or oxcarbazepine therapy as planned. However, as stated above, individuals are considered to be at risk of a severe HLA hypersensitivity reaction "positive" if one or two copies of the variant allele are present, that is, being heterozygous or homozygous for either the *HLA-A*31:01* or *HLA-B*15:02* alleles (Pirmohamed, 2023). These patients should not commence carbamazepine or oxcarbazepine therapy and treatment should be commenced with an alternative drug.

It was noted by a systematic review (Biswas et al., 2022) that patients carrying the *HLA-B*15:02* allele were associated with a significantly increased risk of carbamazepine-related drug hypersensitivity reactions compared to controls in both Asian (OR 14.84; 95% CI 8.95–24.61; p <0.00001) and Caucasian patients (OR 11.65; 95% CI 1.68–80.70; p = 0.01). However, it should be noted that this risk is not absolute; 55% (704/1281; Figure 4 (Biswas et al., 2022)) of patients carrying the *HLA-B*15:02* allele had a carbamazepine related drug hypersensitivity reaction, but approximately 11% (313/2,928; Figure 4 (Biswas et al., 2022)) of patients carrying the *HLA-B*15:02* allele did not have carbamazepine-related severe drug hypersensitivity reactions. Similarly, *HLA-A*31:01* alleles were associated with significantly increased risk of carbamazepine-related drug hypersensitivity reactions (OR 5.92; 95% CI 4.35–8.05; p <0.00001). Again, it should be noted that this risk is not absolute; 20% (163/835; Figure 6 (Biswas et al., 2022)) of patients carrying the *HLA-A*31:01* allele had a carbamazepine-related drug hypersensitivity reaction, but approximately 12% (546/4,450; Figure 6 (Biswas et al., 2022)) of patients carrying the *HLA-B*15:02* allele did not have carbamazepine-related drug reactions. This could lead to a substantial number of patients switching drugs who did not need to and a large number of patients still getting carbamazepine- or oxcarbazepine-related drug reactions despite not being considered at risk based on their genotype at these two SNPs. Also of note, the evidence around *HLA-B*15:02* and *HLA-A*31:01* genotype and oxcarbazepine hypersensitivity is limited. It has been demonstrated that there is an association between *HLA-B*15:02* and SJS/TEN (OR = 27.90) in patients treated with oxcarbazepine. However, this association has not been clearly demonstrated for *HLA-A*31:01* (Chen et al., 2017).

Genotyping would likely use real-time PCR methods, although the proposed item descriptor is method-agnostic so any appropriate genotyping method could be used. During the Pre-PASC teleconference, the applicant mentioned that any method for *HLA-A*31:01* and *HLA-B*15:02* genotyping can use a range of approaches that, e.g., Sequence-Specific Oligonucleotide Probe Hybridization (SSOP) direct Sequencing (NGS), and Sequence-Specific PCR (SSP-PCR). The applicant reported that there were no commercially available kits for testing both the variants described in this application. The applicant also indicated that any kits used for this genotyping would likely be validated by pathology providers in accordance with the

National Pathology Accreditation Advisory Council (NPAAC) standards and notified to the TGA as in-house In Vitro Diagnostic test.

PASC noted that there were potentially additional alleles other than HLA-A*31:01 and HLA-B*15:02 that have been identified as possible predictors of drug hypersensitivity reactions resulting from carbamazepine or oxcarbazepine use. PASC also considered that additional relevant variants could be discovered in the future. PASC considered the evidence base was at present immature for the HTA of the other alleles, although advised a practice note should be added to the proposed MBS item descriptor to futureproof this testing.

PASC noted the applicant's comments that HLA-A*31:01 and HLA-B*15:02 genotyping is typically conducted using polymerase chain reaction (PCR) on DNA extracted from peripheral blood cells (4 ml EDTA sample), with a turnaround time of approximately 5-7 days and testing is conducted in a NATA accredited diagnostic laboratory in accordance with NPAAC guidelines. PASC noted that a positive genotyping result was defined as the presence of at least one copy of either (or both) of the relevant alleles.

PASC noted that drug hypersensitivity reactions in question were typically delayed and occurred within 7-15 days of commencement of drug therapy, resulting in a potentially safe therapeutic window where empirical treatment might be initiated prior to knowing the genotyping outcomes. As a result, PASC considered the proposed genotyping and empirical prescribing of the related drug may occur simultaneously in a proportion of patients in clinical practice, despite clinical guidelines[1] stating genotyping if recommended should be conducted before treatment is commenced. For example, PASC considered that immediate initiation of therapy was particularly important in patients with trigeminal neuralgia who experience severe pain and would require urgent commencement of carbamazepine or oxcarbazepine therapy, and that therefore in practice genotyping would be conducted in parallel to treatment in a proportion of patients. Once the test results are known, the clinician could stop or continue the drug therapy accordingly. PASC further noted that the results of pre-treatment genotyping are not required to be known before commencing treatment in the situation of Thiopurine S-methyltransferase (TPMT) gene testing for thiopurine drugs (MBS item 73327). PASC therefore advised genotyping could be conducted prior to or at commencement of treatment.

Comparator(s)

The comparator is no *HLA-A*31:01 and HLA-B*15:02* genotyping in association with carbamazepine or oxcarbazepine treatment.

The application specified that currently no testing is publicly funded for patients who initiate carbamazepine or oxcarbazepine therapy (p3 of the application form). All patients receive standard-dose carbamazepine or oxcarbazepine and only changes are made once clinical signs of drug hypersensitivity reactions develop.

PASC agreed the comparator was no genotyping.

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[1] The Epilepsy Society of Australia (2009) recommended that in patients of Han-Chinese ethnicity, testing for HLA-B*1502 should be considered prior to prescribing carbamazepine for the first time. The decision to test or not needs to be balanced by test availability, timeliness of the results and urgency of treatment.

Reference standard (for investigative technologies only)

The application did not specify any non-clinical, clinical, or clinical utility standard for comparative analytical performance of the proposed genotyping. The clinical utility standard is proposed to be the ability to predict carbamazepine- or oxcarbazepine-related drug hypersensitivity reactions. There may be some differences in the accuracies and unit costs of different genotyping methods that can be used (e.g. real-time PCR, SSOP, NBS, SSP-PCR) (Fang et al., 2019).

Identifying the *HLA-B*15:02* genotype may present technical difficulties because of the high level of polymorphism among *HLA-B* alleles. Utilising SSP-PCR has been criticised for low clinical accuracy (De Bakker et al., 2006; Zhu et al., 2015). However, another study demonstrated excellent accuracy for a multiplex PCR assay for detection of both *HLA-A*31:01* and *HLA-B*15:02* alleles when compared to a Luminex-SSO/SBT/SSB (Nguyen et al., 2017).

In a study evaluating four screening approaches: multiplex PCR, nested PCR, LAMP, and a novel PCR-dot blot hybridization technique, the methods underwent assessment for their sensitivity, specificity, false positive rates, and operational factors. Each method demonstrated over 99.9% sensitivity and specificity for *HLA-B*15:02* (Jaruthamsophon et al., 2016). In addition, another study using TaqMan assays demonstrated >99.9% sensitivity and >99.9% specificity for *HLA-B*15:02* and *HLA-A*31:01* (Buchner et al., 2021).

PASC agreed the clinical utility standard was the ability to predict carbamazepine- or oxcarbazepine-related drug hypersensitivity reactions.

Outcomes

Safety outcomes:

- Adverse events (AEs) related to *HLA-A*31:01* and *HLA-B*15:02* genotyping.
- AEs (or avoided AEs) from any change in patient management, e.g., treatment modifications, monitoring, any differential potential harms by timing of genotyping (i.e., prior to as versus at commencement of carbamazepine or oxcarbazepine treatment if applicable).

Test performance:

- Prognostic accuracy: Sensitivity, specificity, positive predictive value, and negative predictive value of *HLA-A*31:01* and *HLA-B*15:02* genotyping to predict severe drug hypersensitivity reactions (e.g., SJS, TEN, DRESS or MPE).
- Any differences in prognostic accuracy by patient characteristics (e.g., age, sex, ancestry) and underlying condition (e.g., epilepsy, trigeminal neuralgia, bipolar disorder).

Change in management:

- Change in patient management (e.g., modification of therapy, monitoring).
- Any differences in patient management by patient characteristics (e.g., age, sex, ancestry) and underlying condition (e.g., epilepsy, trigeminal neuralgia, bipolar disorder).

Clinical effectiveness outcomes:

- Direct: Change in patient-relevant health outcomes (e.g., number of SJS, TEN, DRESS or MPE, mortality, morbidity of underlying condition, quality of life) comparing patients who received *HLA-A*31:01* and *HLA-B*15:02* genotyping prior to or at commencement of carbamazepine or oxcarbazepine treatment versus those who did not receive *HLA-A*31:01* and *HLA-B*15:02* genotyping prior to or at commencement of treatment.
- Indirect: Change in patient-relevant health outcomes (e.g., event rates of SJS, TEN, DRESS or MPE, mortality, morbidity of underlying condition, quality of life) in patients who experienced carbamazepine or oxcarbazepine related severe drug hypersensitivity reactions.
- Any harm from *HLA-A*31:01* and *HLA-B*15:02* genotyping, e.g., false negatives; test turn-around time (TAT) resulting in potential delay in commencing treatment in patients who receive pre-treatment testing, or potential delay in stopping treatment in patients who receive concurrent testing and treatment; and false positives leading to unnecessary changes in patient management and potentially less effective therapy.
- Any harm from clinically false negatives (i.e., people who develop a drug hypersensitivity reaction despite a negative genotyping result) and potential harm due to reduced effectiveness of alternative drugs or lack of effective alternative drugs, particularly in trigeminal neuralgia.
- Any differential clinical effectiveness outcomes by patient characteristics (e.g., age, sex, ancestry), and cancer characteristics (e.g., type, stage).
- Any differential clinical effectiveness outcomes by timing of genotyping (prior to as versus at commencement of treatment).

Cost-effectiveness outcomes:

- Cost per patient with positive genotyping result (i.e., *HLA-A*31:01* and/or *HLA-B*15:02* variant) identified.
- Cost per severe drug hypersensitivity reaction avoided.
- Incremental cost per quality-adjusted life year (QALY) gained.
- Any differential results by patient characteristics (e.g., age, sex, ancestry), and cancer characteristics (e.g., location, stage).
- Any differential cost effectiveness results by timing of genotyping (prior to as versus at commencement of treatment).

Health system resources:

- Cost of *HLA-A*31:01* and *HLA-B*15:02* genotyping and associated service costs if applicable.
- Change in the costs associated with the investigation, monitoring, and management of carbamazepine or oxcarbazepine related severe drug hypersensitivity reactions (e.g., drugs, hospitalisation).
- Change in the cost of treatment because of a change in clinical management (e.g., alternative non-carbamazepine or oxcarbazepine-based treatment).
- Any differential impact on resource use and costs by timing of genotyping (prior to as versus at commencement of treatment).
- Total Australian Government healthcare costs.

For the purpose of assessment of false negatives and false positives, it may be appropriate to consider the risk profile as the outcome of the test and not the ability of the test to detect *HLA-A*31:01 and HLA-B*15:02* variants.

PASC considered that the outcomes should include clinically false negatives (i.e., people who develop a drug hypersensitivity reaction despite a negative genotyping result) and potential harm due to reduced effectiveness of alternative drugs or lack of effective alternative drugs, particularly in trigeminal neuralgia.

Assessment framework (for investigative technologies)

Figure 1 provides the assessment framework for *HLA-A*31:01* and *HLA-B*15:02* genotyping in patients about to start carbamazepine or oxcarbazepine therapy.

Figure 1 Assessment framework showing the links from the test population to health outcomes.

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: adverse events due to treatment; 7: adverse events due to testing

CBZ = carbamazepine; OXC = oxcarbazepine

* Drug reaction with eosinophilia and systemic symptoms (DRESS), maculopapular exanthema (MPE), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)

Assessment questions mapped to the assessment framework:

1. What is the comparative safety and effectiveness of *HLA-A*31:01* and *HLA-B*15:02* genotyping (pre-treatment or at treatment commencement) versus no *HLA-A*31:01* and *HLA-B*15:02* genotyping in patients about to commence carbamazepine or oxcarbazepine treatment? (Direct test to health outcomes evidence)
2. What is the diagnostic yield of *HLA-A*31:01* and *HLA-B*15:02* genotyping in patients about to commence carbamazepine or oxcarbazepine treatment? What is the test accuracy of the proposed genotype testing in predicting severe drug hypersensitivity reactions (e.g., SJS, TEN, DRESS or MPE)?
3. How do the proposed genotyping results affect downstream clinical treatment/management (e.g., switching to alternate treatment) and what is the evidence base of the impact?
4. What is the impact of the change in therapy vs no change in therapy on health outcomes such as mortality, morbidities, underlying condition control, and quality of life?

5. What are the effects on safety of changing from carbamazepine or oxcarbazepine to other drugs with regard to adverse events such as severe drug hypersensitivity reactions (e.g., SJS, TEN, DRESS or MPE) and other drug adverse events?
6. How do adverse events of treatment impact on health outcomes (e.g., mortality, quality of life)?
7. What is the comparative safety of *HLA-A*31:01* and *HLA-B*15:02* genotyping (pre-treatment or at treatment commencement) vs. no genotyping including but not limited to e.g., impact of false negative results and potential delay in commencing or stopping treatment due to test turn-around time?

PASC accepted the assessment framework as proposed.

Clinical management algorithms

Figure 2 presents the current clinical algorithm in the application.

Figure 2 Current clinical algorithm (no routine *HLA-A*31:01* or *HLA-B*15:02* genotyping)
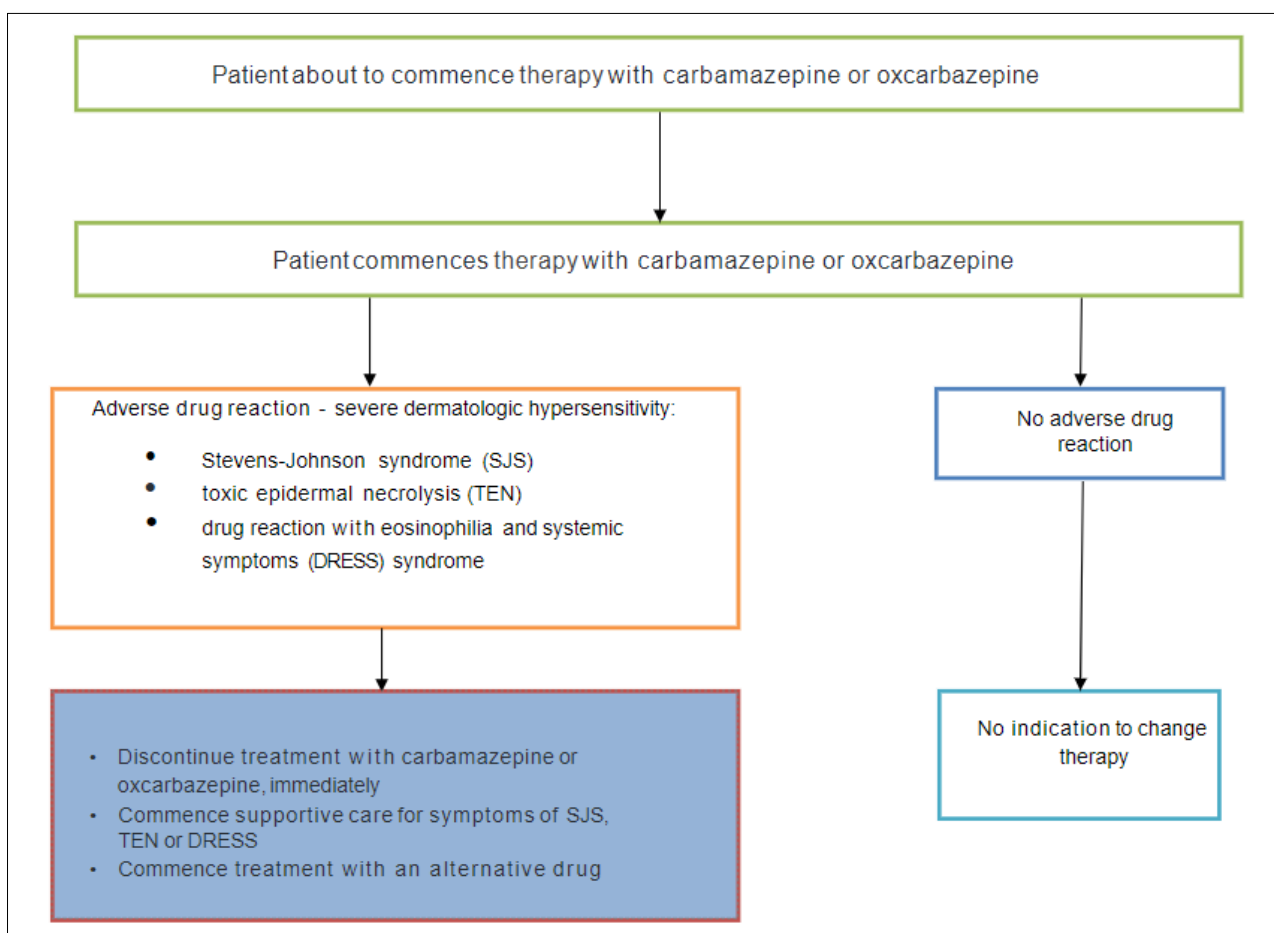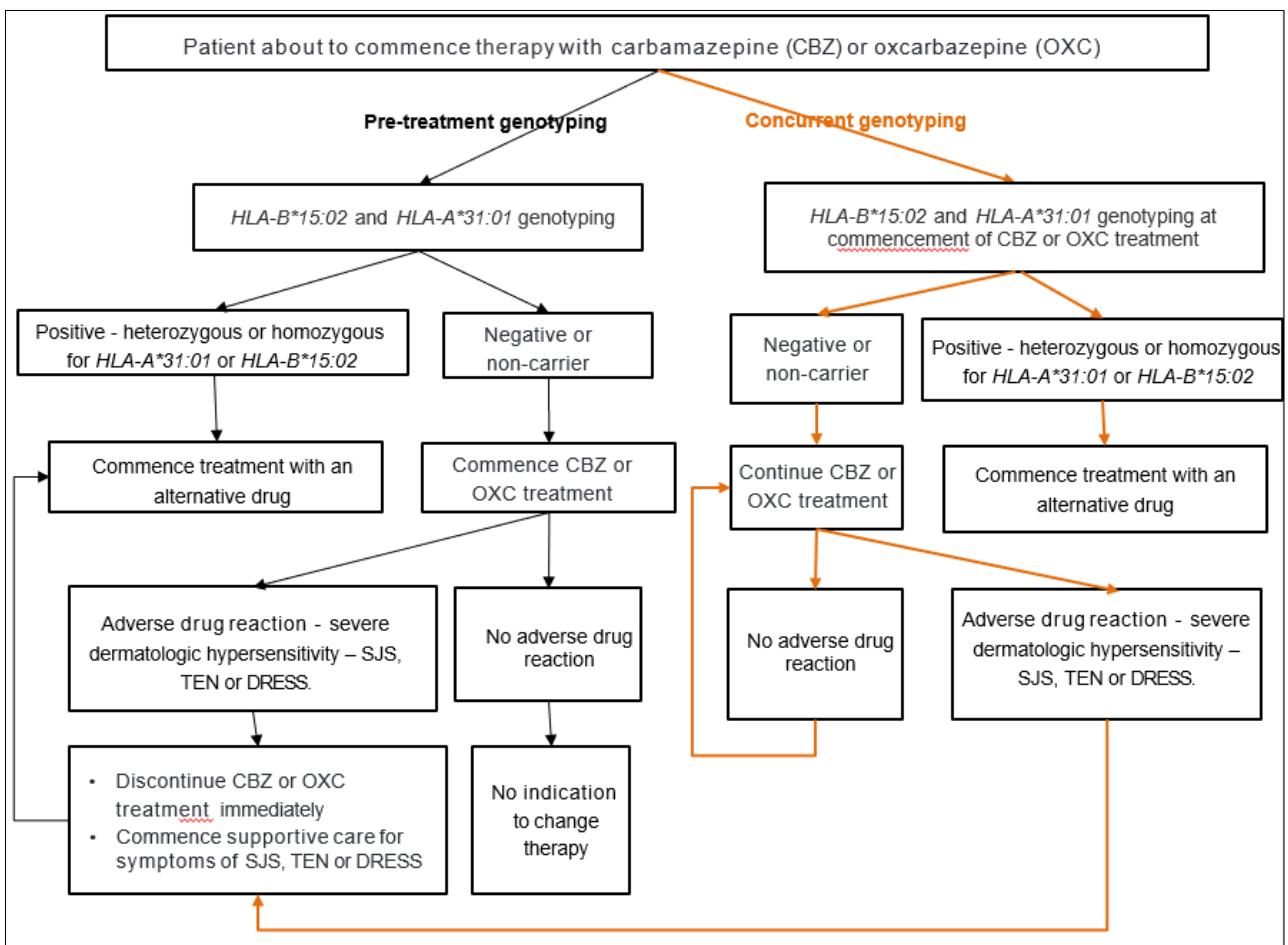

Source: Figure 3, p12 of the PICO set document submitted by the applicant.

As presented, there is currently no routine *HLA-A*31:01* and *HLA-B*15:02* genotyping or any phenotypic testing. Patients would commence treatment with carbamazepine or oxcarbazepine and treatment would cease once signs of a severe drug hypersensitivity reaction were recognised. Patients would then be

switched to a new therapy for their underlying condition and need additional supportive care for their severe drug hypersensitivity reactions.

Figure 3 presents the proposed clinical algorithm, modified from the proposed algorithm in the application to incorporate PASC's advice that genotyping will not always be done prior to initiating treatment, and will be performed concurrently with treatment initiation in some patients. In both the proposed and current algorithms, the population is independent of the underlying condition and focuses on carbamazepine or oxcarbazepine therapy. This may be appropriate; however, there is a need to understand how changes in therapy may affect the underlying condition.

Figure 3 Proposed clinical management algorithm after introducing _HLA-A*31:01_ and _HLA-B*15:02_ genotyping (pre-treatment or at treatment commencement)

Source: Modified from Figure 3, p12 of the PICO set document submitted by the applicant to incorporate PASC's advice.
CBZ = carbamazepine; DRESS = drug reaction with eosinophilia and systemic symptoms; OXC = oxcarbazepine; SJS = Stevens–Johnson syndrome; TEN = toxic epidermal necrolysis.
Arrows in black indicate the clinical management pathway for genotyping prior to carbamazepine or oxcarbazepine treatment while arrows in **orange** indicate the pathway for genotyping at the commencement of carbamazepine or oxcarbazepine treatment.

PASC accepted the clinical management algorithms including modifications to incorporate its advice.

Proposed economic evaluation

The application claimed that pre-treatment *HLA-A*31:01* and *HLA-B*15:02* genotyping was superior to the comparator (no pre-treatment genotyping) in safety and effectiveness. Therefore, the economic evaluation will be a cost-effectiveness analysis (incremental cost per patient with a *HLA-A*31:01 and HLA-B*15:02* variant identified, incremental cost per severe drug hypersensitivity reaction avoided), and cost-utility analysis (incremental cost per QALY gained) (Table 3).

Modelling incremental cost per QALY gained could include the carbamazepine- or oxcarbazepine-related severe drug hypersensitivity reactions and the indication specific health outcomes. Including the change in management and health outcomes for each indication would require indication-specific efficacy results for the alternate treatment chosen for those that were considered at risk for carbamazepine- or oxcarbazepine-related severe drug hypersensitivity reactions. It is likely that this would require more assumptions and therefore could potentially produce highly uncertain results.

Only considering carbamazepine- or oxcarbazepine-related severe drug hypersensitivity reactions could be a simpler and more reliable approach than estimating cost per QALY taking into account indication-specific outcomes. However, restricting the model to only the more certain impacts on utilities (i.e., due to adverse events) would require evidence that changing to an alternate drug therapy did not impact other health outcomes (e.g. seizure freedom, facial pain, etc). Under similar Application 1760 – DPYD genotyping to predict fluoropyrimidine-induced toxicity, PASC *"noted the Assessment Group recommended limiting the scope of the economic model to the impact on adverse events, including death and disutilities associated with adverse events. PASC considered the economic model should be developed following the evidence as per usual"*, and *"advised that in the absence of robust evidence that there was no consequence of dose reduction on cancer outcomes, excluding the impact on cancer outcomes would also produce highly uncertain results. PASC considered that stepped presentation of the economic results (i.e. including all QALY types but with less attention to the less certain ones) may sufficiently clarify the uncertainty to be informative for decision-making"* (1760 PICO, pg. 28). Therefore, a stepped presentation of the economic results (i.e. including all QALY types) is also proposed to be used in the assessment of this application.

An exemplar indication could be used to simplify the model, however PASC considered under Application 1760 that data may be scarce to inform a large model through to health outcomes, and so advised a heterogeneous combination of indications should be used rather than an exemplar, to allow the most data to inform the model. Also there are more indications for carbamazepine than for fluoropyrimidines.

Based on the clinical claim of superior health outcomes compared to the current standard of care, a cost-effectiveness or cost-utility analysis would be appropriate (Table 3). It is likely that the test would lead to superiority in terms of comparative safety (due to a reduction in carbamazepine or oxcarbazepine severe drug hypersensitivity reactions) and non-inferior in terms to clinical outcomes due to continued treatment with other medications.

PASC noted that there are multiple indications for treatment with carbamazepine or oxcarbazepine, but considered that epilepsy is lifelong whereas trigeminal neuralgia is relapsing and remitting. PASC noted that the applicant and the assessment group agreed these two indications were the more important ones to understand for this application. In order to simplify the assessment, PASC advised the economic

evaluation could therefore use two exemplars: epilepsy and trigeminal neuralgia. PASC requested that the analysis include a stepped approach.

PASC noted the applicant had made a clinical claim that genotyping would have superior effectiveness but considered that superior effectiveness would mean that carbamazepine or oxcarbazepine would become more effective at treating the primary indication (e.g. epilepsy or trigeminal neuralgia), whereas alternative treatments may be less effective at managing the primary indication. PASC considered the claim of superior safety appeared reasonable as genotyping would potentially prevent adverse events from drug treatment. PASC considered the clinical claim would therefore more likely be for superior safety and inferior effectiveness, although the conclusion of the clinical claim would depend on the evidence identified in the assessment stage.

Following PASC consideration that the proposed genotyping would occur at the commencement of carbamazepine or oxcarbazepine treatment in a proportion of patients in clinical practice, the question of interest for the economic evaluation is: What is the comparative cost-effectiveness of genotyping (pre-treatment or at treatment commencement) to identify HLA-A and HLA-B alleles (HLA-A*31:01 and HLA-B*15:02) versus no genotyping in patients about to commence first carbamazepine or oxcarbazepine treatment?

Table 3   Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	**Uncertain[a]**	**Noninferior[b]**	**Superior**
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

Proposal for public funding

The applicant proposed *HLA-A*31:01* and *HLA-B*15:02* genotyping be publicly funded through the MBS. In the application form, the applicant proposed an MBS item descriptor for pathology services. The applicant proposed the following item descriptor (Table 4).

Table 4 Applicant proposed MBS item descriptor

Category 6 – PATHOLOGY SERVICES	Group P7 – Genetics
MBS item AAAA Genotyping of a patient in line with current guidelines, including at least *HLA-B*15:02* and *HLA-A*31:01* variants but not limited to, prior to the initiation of treatment with the anticonvulsant drug and analgesic drug, carbamazepine, requested by a specialist or consultant physician. Once per lifetime	
Fee: $188	

Source: p11 of the application

During PICO development, the proposed item descriptor was updated to be in line with more standard MBS wording (Table 5), and to incorporate the applicant's advice at the pre-PASC teleconference that oxcarbazepine should also be included, and that genotyping should not be restricted based on treatment indication.

Table 5 MBS item descriptor proposed during PICO development

Category 6 – PATHOLOGY SERVICES	Group P7 – Genetics
MBS item AAAA Genetic testing for *HLA-B*15:02* and *HLA-A*31:01* variants to predict risk of carbamazepine- or oxcarbazepine-related severe drug hypersensitivity reactions in a patient, where; a. the service is requested by a specialist or consultant physician; and b. 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	

Source: p11 of the application, updated during development of the PICO confirmation

There was no justification provided for the proposed fee. The proposed fee is the same as the proposed fee in similar application 1760, 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 fee is much higher than MBS item 73320 ($40.55) for detection of *HLA-B27* by nucleic acid amplification, MBS item 73317 ($36) for detecting genetic mutations for haemochromatosis and MBS item 71151 ($118.85) for phenotyping 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.

PASC considered that genetic counselling is not required in association with this testing, because although the genotypes being tested for are heritable, they only become relevant when a person commences a relevant drug. PASC therefore advised an explanatory note regarding genetic counselling was not necessary.

PASC noted the applicant had proposed a fee of $188, which aligned with the fee proposed for genotyping in similar application 1760 but was higher than the fee for existing MBS item 73320 to genotype one HLA SNP (HLA-B27). PASC noted the applicant's comments that the genotyping for the two proposed HLA variants requires two separate tests that cannot easily be done together, increasing the resources required for the combined testing. PASC accepted the applicant's advice and advised the assessment report's base case to use the applicant's proposed fee but explore the impact of the fee on the cost-effectiveness and cost as per usual.

PASC considered that requestors should not be restricted to specialists, because general practitioners also initiate prescribing these drugs, especially in cases of trigeminal neuralgia, and restricting requestors of this testing could reduce access through primary care.

As above, PASC considered that while clinical guidelines recommend genotyping be conducted prior to commencing treatment, this would not take place in practice for a proportion of the patients in this population, such as those in severe pain from trigeminal neuralgia. PASC therefore considered the MBS item descriptor should be silent with respect to the timing of genotyping (i.e., prior to or at treatment commencement) to allow both as is clinically appropriate.

PASC noted genotyping was only proposed for patients in relation to their first treatment with carbamazepine or oxcarbazepine. PASC considered once a patient has used one of these medicines for the first time without a hypersensitivity reaction, they would not need to receive this genotyping prior to subsequent treatments, and that it may reduce leakage for either the item descriptor or a practice note to specify that this testing is to be done only in relation to the patient's first use of one of these medicines.

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 insufficiently futureproofed. 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 may also encompass any other alleles that are identified in the future as needing to be included in this testing.

Table 6 presents the MBS item descriptor supported by PASC.

Table 6 PASC's revised MBS item descriptor

Category 6 – PATHOLOGY SERVICES	Group P7 – Genetics
MBS item AAAA Genetic testing for HLA variants to predict risk of carbamazepine- or oxcarbazepine-related severe drug hypersensitivity reactions in a patient initiating first 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) *HLA-B*15:02* and *HLA-A*31:01.*	

PASC noted a potential unintended consequence that the proposed pre-treatment HLA genotyping if approved might result in more widespread mandatory pre-treatment HLA testing in clinical practice, beyond the drugs listed in the proposed MBS item descriptor. An example was HLA genotyping before treatment with trimethoprim + sulfamethoxazole where the genotyping might also predict risk of SJS. PASC considered that addressing the issue of clinicians' prescribing behaviour was outside MSAC's remit, and that standard processes were in place to monitor utilisation and address potential leakage issue.

Summary of public consultation input

PASC noted and welcomed consultation input from 6 organisations and 1 individual who identified himself as medical director for laboratories that perform HLA typing. The 6 organisations that submitted input were:

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

The consultation feedback received was supportive.

Clinical need and public health significance

The main benefits of public funding received in the consultation feedback included the ability to prevent the occurrence of severe cutaneous reactions including the hospitalisations, reduce morbidity and mortality, allow clinicians to consider alternate medicines and remove financial barriers to access the test.

The consultation feedback raised a concern in relation to short delays in the treatment commencement while waiting for the results of the proposed test. Absence of risk variants characterised in the proposed service does not eliminate the risk of hypersensitivity to the drug and patient can still experience the severe adverse side effects.

ASCEPT asserted that there is no inherited disease related implications and no benefit of genetic counselling, but positive test result report should advise referral to genetic counselling if the patient has concerns about familial implications.

Indication(s) for the proposed medical service and clinical claim

The consultation feedback mostly agreed with the proposed population. RANZCP and ASCEPT advocated not to limit the indication to epilepsy and trigeminal neuralgia and expand indications to include all patients prescribed carbamazepine. Feedback from RANZCP and ACD acknowledged the high prevalence of risk HLA alleles in Asian population, noting lower prevalence in other populations including Caucasians. ASCEPT advocated not to limit the test to one ancestry and highlighted the risk of ethnicity assumptions due to diverse ancestry of the Australian population.

The consultation feedback strongly agreed with the proposed comparator.

The consultation feedback agreed with the clinical claim for genotyping the HLA alleles, and considered there is considerable evidence is available to prove the superiority claim.

Cost information for the proposed medical service

The consultation feedback agreed with the proposed service descriptor supported an item that could include additional known HLA risk variants (e.g., *HLA-B*15:11*, *HLA-A* 11:01*, *HLA-B*15:21*, *HLA-B*15:08* in some populations). 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 consultation feedback agreed with the proposed service fee. Respondent highlighted the existence of two MBS item with lower service fees for a more 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 the $188 fee is a more realistic representation of the current cost of providing this testing. 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.

Consumer Feedback

PASC noted that the public consultation input received was generally supportive.

Next steps

PASC advised that, upon ratification of the post-PASC PICO, the application can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process. PASC noted the applicant has elected to progress its application as a DCAR (Department-Contracted Assessment Report).

PASC noted the assessment group's concern regarding the evidence on individual genotype results. Most of the relevant evidence describes the risk associated with testing one of the proposed SNPs individually. The risks associated with testing both SNPs together are mostly unknown and may need to be calculated during evaluation through sourcing raw data from relevant sources. PASC noted the assessment group commented that although this would not exceed the scope of a DCAR, it anticipated additional time would

nonetheless be required to contact the study authors to obtain the aforementioned data relating to combined genotypes for the DCAR. PASC noted the applicant agreed to additional time being taken for the preparation of this DCAR.

Applicant Comments on Ratified PICO

The applicant had no comments.

References

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