HLA: carbamazepine 6237/6238/6239

95% CI = 95% confidence interval, DOR = diagnostic odds ratio, DRESS = drug reaction with eosinophilia and systemic symptoms, also known as hypersensitivity syndrome (HSS), HSS = hypersensitivity syndrome, including DRESS, MPE = maculopapular exanthema, NS = not significant, OR = odds ratio, S = significant, SJS = Stevens-Johnson syndrome, SmPC = summary of product characteristics, TEN = toxic epidermal necrolysis

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, then the health care professional should consider the next best option.

Brief summary and justification of choices:
Carbamazepine can induce the life-threatening cutaneous adverse events SJS/TEN (in 0.25% of the Chinese users and 0.005% of European users) and DRESS (in 0.05% of both Chinese and European users). In addition, carbamazepine can induce mild maculopapular exanthema (in 4.4% of Chinese and 10% of White users). The hypersensitivity reactions generally develop between 2 weeks and 3 months after the start of carbamazepine.
Because specific HLA proteins are involved in specific cellular immune reactions that cause specific hypersensitivity reactions, HLA proteins can affect the risk of hypersensitivity reactions.
HLA-B*1502
HLA-B*1502 is present at a frequency of more than 1% only in persons of Southeast Asian ancestry (Han Chinese, Thai, Malaysians, Indians).
Six meta-analyses showed that this allele strongly increased the risk for carbamazepine-induced SJS/TEN (OR = 27-138) (Sukasem 2021, Chouchi 2018, Bloch 2014, Grover 2014, Tangamornsuksan 2013, and Yip 2012). In addition, one study in Han Chinese showed that excluding HLA-B*1502 positive patients from therapy with carbamazepine, resulted in reduction of the incidence of carbamazepine-induced SJS/TEN from 0.23% to 0% (Chen 2011).
For this reason, the KNMP Pharmacogenetics Working Group concluded that there is a gene-drug interaction and that therapy adjustment is required (yes/yes-interaction).
HLA-A*3101
HLA-A*3101 is present at a frequency of more than 1% in both Asians and Europeans.
Seven meta-analyses (2 for DRESS, 3 for SJS/TEN, 1 for MPE and 1 for all cutaneous adverse events) and a meta-analysis of genome wide association studies (GWAS) for severe cutaneous adverse events (DRESS, SJS/TEN or acute generalized exanthematous pustulosis (AGEP)) showed that this allele increased the risk for carbamazepine-induced cutaneous adverse events (Nicoletti 2019, Genin 2014, Bloch 2014, Grover 2014, and Yip 2012). The meta-analyses found the strongest effect for DRESS (OR = 10.2-13.2 for all ethnicities and OR = 24.1 for Europeans) (Genin 2014 and Grover 2014). For SJS/TEN, the OR was 3.9-8.0 (7.9 for Europeans) (Genin 2014, Bloch 2014, and Grover 2014). For all severe cutaneous adverse events, the OR was 8.0 in Europeans (Nicoletti 2019). For MPE and all cutaneous adverse events, the OR was respectively 7.2 and 9.5 (Grover 2014 and Yip 2012).
In addition, one study in Japanese showed that excluding the 17.7% HLA-A*3101 carriers from therapy with carbamazepine, resulted in reduction of the incidence of carbamazepine-induced cutaneous adverse events from 3.4% to 2.0% (Mushiroda 2018).
For Europeans/Whites the positive predictive value was 0.89% for DRESS (Genin 2014). The positive predictive value for all cutaneous adverse events was 7.9% (Mushiroda 2018). Note: Yip 2012 calculated a higher positive predictive value for all cutaneous adverse events for Europeans (43%) than for Japanese (12%), based on a higher incidence of cutaneous adverse events in Europeans. However, this higher incidence of cutaneous adverse events in Europeans is unlikely to be caused by HLA-A*3101 that has a higher frequency in Japanese than in Europeans.
Although the positive predictive value for DRESS is not high, the increase in risk is considerable and life-threatening adverse events should be avoided if possible. For these reasons, the KNMP Pharmacogenetics Working Group concluded that there is a gene-drug interaction and that therapy adjustment is useful (yes/yes-interaction).
HLA-B*1511
HLA-B*1511 is present at a frequency of more than 1% only in some specific Asian populations (Han Chinese, Koreans, Thai).
Two meta-analysis showed that this allele increased the risk for carbamazepine-induced SJS/TEN (OR = 14-17) (Wang 2017 and Grover 2014).

Because the increase in risk is considerable and life-threatening adverse events should be avoided if possible, the KNMP Pharmacogenetics Working Group concluded that there is a gene-drug interaction and that therapy adjustment is useful (yes/yes-interaction).

HLA-B*5101

One meta-analysis suggested that HLA-B*5101 slightly increased the risk for carbamazepine-induced cutaneous adverse advents (OR = 1.7), but did not confirm this for the separate cutaneous adverse events (SJS/TEN, HSS/MPE, and HSS) (Grover 2014). A second meta-analysis confirmed the absence of an increased SJS/TEN risk (Wang 2017).

Based on this, the KNMP Pharmacogenetics Working Group concluded that there was not enough evidence for a HLA-B*5101-carbamazepine interaction. So, there was not enough cause for inclusion of this gene-drug combination in the electronic decision support systems and/or the KNMP Kennisbank.

HLA-B*4001, HLA-B*5801, HLA-A*2402 and HLA-B*4601

Two meta-analyses showed that HLA-B*4001 and HLA-B*5801 decreased the risk for carbamazepine-induced SJS/TEN (OR = 0.14 in Chinese and OR = 0.22 for HLA-B*4001 and OR = 0.23-0.38 for HLA-B*5801) (Wang 2017 and Grover 2014).

One meta-analysis showed that HLA-A*2402 decreased the risk for carbamazepine-induced SJS/TEN (OR = 0.27) (Grover 2014).

One meta-analysis showed that HLA-B*4601 decreased the risk for carbamazepine-induced SJS/TEN (OR = 0.49), but another meta-analysis did not find an effect (Wang 2017 and Grover 2014).

Because the observed effect is positive, no action is required. In addition, according to Wang 2017, these alleles did not fully prevent SJS/TEN. 4.2% of the SJS/TEN cases had HLA-B*5801, 9.4% HLA-B*4001 and 16.5% HLA-B*4601. This strongly limits the clinical applicability of information on the presence or absence of these alleles. For these reasons, the KNMP Pharmacogenetics Working Group decided that there was not enough cause for inclusion of these gene-drug combinations in the electronic decision support systems and/or the KNMP Kennisbank.

HLA-B*1301, HLA-B*3802, HLA-B*5502, HLA-B*5601, HLA-A*0201, HLA-A*1101, HLA-A*3303, HLA-B*0702, HLA-B*1501, HLA-B*1518, HLA-B*4002, HLA-B*1525, HLA-B*3505, HLA-B*5102, HLA-B*5401, and HLA-B*5701

Two meta-analysis found no effect of HLA-B*1301, HLA-B*3802, HLA-B*5502, and HLA-B*5601 on the risk of carbamazepine-induced cutaneous adverse events (Wang 2017 and Grover 2014).

One meta-analysis found no effect of HLA-A*0201, HLA-A*1101, HLA-A*3303, HLA-B*0702, HLA-B*1501, HLA-B*1518, HLA-B*4002 (Grover 2014), HLA-B*1525, HLA-B*3505, HLA-B*5102, HLA-B*5401 (Wang 2017), and HLA-B*5701 (Nicoletti 2019) on the risk of carbamazepine-induced cutaneous adverse events.

Therefore, the KNMP Pharmacogenetics Working Group decided that there was not enough cause for inclusion of these gene-drug combinations in the KNMP Kennisbank.

For the included interactions between carbamazepine and HLA genotype groups (HLA-B*1502, HLA-A*3101 and HLA-B*1511 carriers), you can find an overview of the observed effects per genotype group in the background information text of the corresponding gene-drug interactions in the KNMP Kennisbank. You may also have access to this background information text via your pharmacy or physician electronic decision support system.

The justification for the therapeutic recommendations for these genotype groups is provided below.

Therapeutic recommendations

For HLA-B*1502, the recommendation is to choose an alternative. If an alternative is possible, choosing an alternative is also recommended for HLA-A*3101 and HLA-B*1511.

Although an association was found between HLA-B*1502 and SJS/TEN induced by phenytoin, lamotrigine and oxcarbazepine, the risk for SJS/TEN in HLA-B*1502-positive users of these antiepileptic drugs was approximately 10-fold lower compared to HLA-B*1502-positive users of carbamazepine. The cost-effectiveness analysis of Chen 2016 calculated positive predictive values for SJS/TEN in HLA-B*1502-positive patients of 6.7% for carbamazepine and 0.65% for phenytoin (Chen Z et al. Real-world cost-effectiveness of pharmacogenetic screening for epilepsy treatment. Neurology 2016;86:1086-94. PubMed PMID: 26888992). The calculated positive predictive value for SJS/TEN in HLA-B*1502-positive Taiwanese patients was 0.73% for oxcarbazepine and 7.7% for carbamazepine (Chen CB et al. Risk and association of HLA with oxcarbazepine-induced cutaneous adverse reactions in Asians. Neurology 2017;88:78-86 and Hung SI et al. HLA-B genotyping to detect carbamazepine-induced Stevens-Johnson syndrome: implications for personalizing medicine. Personalized Med 2005;2:225–37). In addition, the most severe forms of SJS/TEN (SJS/TEN-overlap and TEN) were not observed with oxcarbazepine. For lamotrigine, the association of HLA-B*1502 was similar in strength as that for phenytoin (OR = 3.6 for lamotrigine and OR = 3.5-5.3 for phenytoin). Despite the fact that lamotrigine and oxcarbazepine were also used as alternative medication for HLA-B*1502 carriers in the study of Chen 2011, no cases of SJS/TEN were observed.

Recommendation concerning pre-emptive genotyping, including justification of choices:

The KNMP Pharmacogenetics Working Group considers HLA-B*1502 genotyping of patients of Asian, other than Japanese descent, HLA-A*3101 genotyping, and HLA-B*1511 genotyping of patients of Han Chinese, Korean, Thai or Japanese descent before starting carbamazepine to be beneficial for drug safety. It is advised to consider genotyping these patients before (or directly after) drug therapy has been initiated to guide drug selection.

HLA-B*1502

HLA-B*1502 has not been detected in a sample of 1350 Dutch persons (Allele Frequency Net Database: http://www.allelefrequencies.net). For this reason, the KNMP Pharmacogenetics Working Group does not consider HLA-B*1502 genotyping of Dutch patients in general before starting carbamazepine to be useful. However, the HLA-B*1502 frequency is high in persons of Asian descent, other than Japanese. In Japanese the HLA-B*1502 frequency

is very low (< 0.1%). In Korea, it is less than 1% in some populations and more than 1% in other populations, with a mean of approximately 2% according to the SmPC of carbamazepine.
The clinical implication of the HLA-B*1502-carbamazepine interaction scores 7 out of the maximum of 10 points for patients of Han Chinese or Thai descent and 6 out of the maximum of 10 points for patients of Asian, other than Japanese, Han Chinese or Thai, descent. Pre-emptive genotyping is considered to be essential for scores ranging from 6 to 10 points (see below and the clinical implication score tables at the end of this risk analysis). However, the KNMP Pharmacogenetics Working Group decided to downgrade the score, because there might not be an equivalent alternative for carbamazepine and the positive predictive value of HLA-B*1502 for severe cutaneous adverse events is low. Carbamazepine is a commonly used drug and is prescribed for epilepsy, trigeminal neuralgia and bipolar disorder. For all of these indications, effectiveness of drugs is patient specific. As a result, excluding one of this drugs diminishes the chance of finding an effective treatment. Because the positive predictive value of HLA-B*1502 carriage for development of carbamazepine-induced severe cutaneous adverse events is low (1.8-7.7% according to Yip 2012 and Hung SI et al. HLA-B genotyping to detect carbamazepine-induced Stevens-Johnson syndrome: implications for personalizing medicine. Personalized Med 2005;2:225–37, which correlates well with the positive predictive value of 3.0% derived from the genotype-guided study of Chen 2011), a large majority of HLA-B*1502 carriers will be falsely denied carbamazepine. So, pre-emptive genotyping will not only diminish severe adverse events, but will also strongly increase the number of patients who are falsely denied a commonly used drug for the treatment of epilepsy, trigeminal neuralgia and bipolar disorder. For this reason, the KNMP Pharmacogenetics Working decided that genotyping for HLA-B*1502 in patients planned to be started on carbamazepine is not essential and downgraded the recommendation to beneficial.
The rationale for the (sub)scores of the clinical implication score is indicated below:
HLA-B*1502 has been shown to strongly increase the risk of the severe and possibly life-threatening cutaneous adverse event SJS/TEN (code E corresponding to CTCAE grade 4). This results in 1 out of the maximum score of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (1 point for code D or E (CTCAE grade 3 or 4)).
Six meta-analyses (with a maximum of 15 studies per meta-analysis) showed that HLA-B*1502 increased the risk of carbamazepine-induced SJS/TEN. This results in the maximum of 3 points for the second criterion of the clinical implication score, the level of evidence supporting the associated clinical effect grade ≥ 3 (3 points for at least three publications with level of evidence score ≥ 3).
A study in Taiwanese showed that excluding HLA-B*1502 positive patients from therapy with carbamazepine resulted in reduction of the incidence of severe cutaneous adverse events from 0.23% to 0% (Chen 2011). This corresponds to a number needed to genotype of 435 to avoid one severe cutaneous adverse event in this Taiwanese population with a HLA-B*1502 carrier frequency of 7.7%. For many other Southeast Asian populations (Han Chinese, Thai, Malaysians, Indians), the HLA-B*1502 carrier frequency is reported to be higher than or similar to 7.7%. So, a number needed to genotype of 435 seems to be a good representation for the upper limit in Southeast Asians. According to the SmPC, the HLA-B*1502 allele frequency in Koreans is recently reported to be 2%, corresponding to a carrier frequency of 4%, which would result in a number needed to genotype of approximately 837. A number needed to genotype of 435-837 results in 1 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) to prevent one clinical effect code ≥ D (grade ≥ 3) (1 point for 100 < NNG ≤ 1000).
The SmPC of carbamazepine indicates that before deciding to start treatment and if possible, patients of Han Chinese or Thai ancestry should be screened for HLA-B*1502. In addition, the SmPC indicates that because of the prevalence of HLA-B*1502 in other Asian populations (for instance more than 15% in the Philippines and Malaysia and recently reported allele frequencies of 2% and 6% respectively in Korea and India), one can consider testing patients from risk populations for the presence of HLA-B*1502. The SmPC does not mention HLA-B*1502 as a contra-indication for carbamazepine. For patients of Han Chinese or Thai descent, this results in the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (2 points for a recommendation to genotype in the SmPC). For patients of other Asian, non-Japanese, descent, this results in 1 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/phenotype being mentioned in the SmPC, but not mentioned as a contra-indication and no recommendation to genotype).
Note: While the DPWG considers genotyping of HLA-B*1502 in patients of Asian, other than Japanese descent, to be beneficial, 4 out of 7 cost-effectiveness or cost analyses and a review of the 3 oldest analyses suggest genotyping to be cost-effective in patients of South-Asian or Southeast-Asian ancestry (Zhou 2021, Choi 2019, Tiamkao 2013, Dong 2012, and Plumpton 2016). Of the remaining 3 cost-effectiveness analyses, 2 suggested cost-effectiveness at a higher willingness-to-pay threshold (Yuliwulandari 2021 and Rattanavipapong 2013). However, of the two cost-effectiveness analyses that also included the relative therapeutic effectiveness of carbamazepine and its alternative in the calculation, only the one with the more effective alternative (levetiracetam) (Choi 2019) and not the one with the less effective alternative (valproic acid) (Chong 2017), found genotype-guided therapy to result in an increase of quality-adjusted life years compared to carbamazepine for all. This emphasizes the importance of the availability of an efficient alternative, because the large majority of HLA-B*1502 carriers will be falsely denied carbamazepine. In this regard, it supports the downgrading of the recommendation from essential to beneficial by the KNMP Pharmacogenetics Working Group due to the uncertainty of availability of an equivalent alternative for carbamazepine for HLA-B*1502 carriers.

<u>HLA-A*3101</u>

The clinical implication of the gene-drug interaction scores 5 out of the maximum of 10 points (with pre-emptive genotyping considered to be beneficial for scores ranging from 3 to 5 points):

HLA-A*3101 has been shown to increase the risk of the severe and possibly life-threatening cutaneous adverse events SJS/TEN and DRESS (code E corresponding to CTCAE grade 4). This results in 1 out of the maximum score of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (1 point for code D or E (CTCAE grade 3 or 4)).
Five meta-analyses (with a maximum of 8 studies per meta-analysis) (2 for DRESS and 3 for SJS/TEN) showed that this allele increased the risk for severe carbamazepine-induced cutaneous adverse. This results in the maximum of 3 points for the second criterion of the clinical implication score, the level of evidence supporting the associated clinical effect grade ≥ 3 (3 points for at least three publications with level of evidence score ≥ 3).
Carbamazepine can induce the life-threatening cutaneous adverse events SJS/TEN in 0.005% of European users and DRESS in 0.05% of European users, so severe cutaneous adverse events in 0.055%. This indicates that even if HLA-A*3101 would be the only cause of carbamazepine-induced severe cutaneous adverse events, a minimum of 1818 patients would have to be genotyped to prevent one case of carbamazepine-induced severe cutaneous adverse events. Because the number needed to genotype to prevent 1 adverse event code ≥ D (grade ≥ 3) is larger than 1000, this results in 0 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) to prevent one clinical effect code ≥ D (grade ≥ 3) (only points for NNG ≤ 1000).
The Summary of Product Characteristics (SmPC) contains a warning that there are some data indicating that HLA-A*3101 in European populations is possibly associated with an increased risk of carbamazepine-induced cutaneous adverse events, including SJS, TEN, and drug-induced rash with eosinophilia (DRESS), but does not mentions HLA-A*3101 as a contra-indication for carbamazepine and indicates that there is insufficient evidence to recommend screening for the presence of HLA-A*3101 before starting treatment with carbamazepine. This results in 1 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/phenotype mentioned in the SmPC, but not mentioned as a contra-indication and no recommendation to genotype).
Note: While the DPWG considers genotyping of HLA-B*A*3101 to be beneficial, both the cost-effectiveness analyses performed for the UK population and the analysis estimating cost-effectiveness globally, suggest genotyping to be cost-effective (Plumpton 2019, Plumpton 2016, Plumpton 2015, and Zhou 2021). However, these analyses assumed the alternative antiepileptic drug to be equally effective as carbamazepine.

<u>HLA-B*1511</u>

HLA-B*1511 has not been detected in a sample of 1350 Dutch persons (Allele Frequency Net Database: http://www.allelefrequencies.net). For this reason, the KNMP Pharmacogenetics Working Group does not consider HLA-B*1511 genotyping of Dutch patients in general before starting carbamazepine to be useful. However, HLA-B*1511 is present at a frequency of 1% or more only in some specific Asian populations (Han Chinese, Koreans, Thai). In Japanese and Taiwanese, the HLA-B*1511 frequency is low (< 1%) and in Malaysians very low (< 0.3%). Despite the frequency in Japanese being low, 2 of the 4 studies the meta-analysis of Wang 2017 showing HLA-B*1511 to increase SJS/TEN risk were Japanese, with one of them showing a significant risk increase itself. For this reason, the HLA-B*1511 genotyping recommendation was extended to Japanese patients. Because most Taiwanese are Han Chinese, Taiwanese patients were already included.
The clinical implication of the HLA-B*1511-carbamazepine interaction scores 4 out of the maximum of 10 points for patients of Han Chinese, Korean, Thai or Japanese descent. Pre-emptive genotyping is considered to be beneficial for scores ranging from 3 to 5 points (see below and the clinical implication score tables at the end of this risk analysis).
HLA-B*1511 has been shown to increase the risk of the severe and possibly life-threatening cutaneous adverse event SJS/TEN (code E corresponding to CTCAE grade 4). This results in 1 out of the maximum score of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (1 point for code D or E (CTCAE grade 3 or 4)).
Two meta-analyses (with a maximum of 4 studies per meta-analysis) showed that HLA-B*1511 increased the risk for carbamazepine-induced SJS/TEN. Two of the four included studies also showed a significantly increased risk themselves. This results in the maximum of 3 points for the second criterion of the clinical implication score, the level of evidence supporting the associated clinical effect grade ≥ 3 (3 points for at least three publications with level of evidence score ≥ 3).
The highest incidence of carbamazepine-induced SJS/TEN (0.25%) has been observed in Chinese. The meta-analysis of Wang 2017 found HLA-B*1511 in 14% of SJS/TEN cases. Even, when combined with the highest carbamazepine-induced SJS/TEN incidence observed, this would amount to an incidence of only 0.035% for HLA-B*1511 positive SJS/TEN. An incidence of HLA-B*1511 positive SJS/TEN of 0.035% corresponds to a number needed to genotype for HLA-B*1511 to prevent one case of SJS/TEN of 2857. Because the number needed to genotype to prevent 1 adverse event code ≥ D (grade ≥ 3) is larger than 1000, this results in 0 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) to prevent one clinical effect code ≥ D (grade ≥ 3) (only points for NNG ≤ 1000).
The Summary of Product Characteristics (SmPC) of carbamazepine does not mention HLA-B*1511. This results in 0 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (only points for at least one genotype/phenotype mentioned in the SmPC).

Source	Code	Effect	Comments
ref. 1 Sukasem C et al.	3	Meta-analysis of 8 case-control studies in Asians with carbamazepine-tolerant patients as controls. The studies	Author's conclusion:

Spectrum of cutaneous adverse reactions to aromatic antiepileptic drugs and human leukocyte antigen genotypes in Thai patients and meta-analysis. Pharmacogenomics J 2021;21:682-90. PMID: 34175889. **ref. 1, continuation**	B*1502: E	included a total of 224 cases and 524 controls. A random effects model was used for the meta-analysis, but prospective registration of the protocol was not mentioned. The search and selection strategy and the method of data extraction were not mentioned. Quality of the included studies was not assessed. Publication bias analysis was not performed. Results: Association between HLA-B*1502 and SJS/TEN: OR = 137.7 (95% CI: 51.0-372.0) (S) 95% of the cases and 8% of the controls had B*1502. Heterogeneity between the studies was not significant and moderate.	"In meta-analysis, HLA-B*15:02 was associated with SJS/TEN induced by carbamazepine (OR 137.69, 95% CI 50.97-371.98, p < 0.001)."
ref. 2 Nicoletti P et al. Shared genetic risk factors across carbamazepine-induced hypersensitivity reactions. Clin Pharmacol Ther 2019;106:1028-36. PMID: 31066027.	3 A*3101: E	Meta-analysis of 2 genome-wide association studies (GWAS) in Europeans. The GWAS included a total of 43 carbamazepine-induced severe cutaneous adverse reaction cases and 10,701 population controls. Of the 43 cases, 25 had DRESS, 16 SJS/TEN and 2 acute generalized exanthematous pustulosis (AGEP). A fixed effects model was used for the meta-analysis, whereas a random effects model should be chosen when presence of heterogeneity cannot be excluded. The search and selection strategy was not mentioned, but the method of data extraction was transparent. Quality of the included GWAS was not scored. Each GWAS was performed in a logistic regression framework, under an additive genetic model (i.e. assuming a stronger effect in homozygotes than in heterozygotes), with adjustment for the first twelve or first seven principal components to account for population structure. No other additional covariates were included in the model. To account for the small sample size and the disproportionate case/control ratio, a permutation approach for genomewide significant signals was performed. Selection bias analysis was not performed. Results: Associations with serious cutaneous adverse reactions: The strongest association signal mapped to the major histocompatibility complex (MHC (the HLA gene region); lead SNP (single nucleotide polymorphism) rs192543598; OR = 18.1; 95% CI 8.03-40.90; P = $1.7x10^{-12}$; $P_{perm} < 5x10^{-8}$ (indicating genomewide significance) (S). This SNP was in strong linkage disequilibrium with HLA-A*3101 ($r^2 = 0.75$). HLA-A*3101 also reached genomewide significance in the meta-analysis (OR = 8.0; 95% CI 4.10-15.80; P = $2.2x10^{-9}$; $P_{perm} < 5x10^{-8}$). In addition, reciprocal conditional analyses demonstrated that rs192543598 and HLA-A*3101 represent the same underlying association signal. Heterogeneity between the GWAS was not significant for HLA-A*3101, but there was a trend (P = 0.11). The HLA-A*3101 association was less significant in the broadly European cases than in the British cases, probably because of greater heterogeneity in their geographic origin. A lower allele frequency was observed in the Spanish cases (6%) compared with other ethnic groups (15% in Northern European and 13% Italian cases) despite an equivalent frequency in the three control groups. However, the effect of HLA-A*3101 was conserved in all European populations ($OR_{Italian}$ = 8.7; $OR_{Spanish}$ = 3.66; and $OR_{North\ Europeans}$ = 5.51). The HLA-A*3101 association was genomewide significant in the DRESS subgroup (OR = 12.9; 95% CI 5.58-	Author's conclusion: "HLA-A*31:01 was identified as the strongest genetic predisposing factor for both CBZ-SCAR (odds ratio (OR) = 8.0; 95% CI 4.10-15.80; P = 1.2×10^{-9}) and CBZ-DILI (OR = 7.3; 95% CI 2.47-23.67; P = 0.0004) in European populations. The association with HLA-A*31:01 in patients with SCAR was mainly driven by hypersensitivity syndrome (OR = 12.9; P = 2.1×10^{-9}) rather than by Stevens-Johnson syndrome/ toxic epidermal necrolysis cases, which showed an association with HLA-B*57:01."

<table>
<tr><td>ref. 2, continuation</td><td>B*5701: AA</td><td>29.78; P = 2.1x10^{-9}), but not in the SJS/TEN subgroup.
There was an MHC-region-wide significant, but not genomewide significant, association with HLA-B*5701 in the SJS/TEN subgroup (OR = 6.2; 95% CI 2.47-15.37; P = 9.9x10^{-5}).</td><td></td></tr>
<tr><td>ref. 3
Mushiroda T et al. Association of HLA-A*31:01 screening with the incidence of carbamazepine-induced cutaneous adverse reactions in a Japanese population.
JAMA Neurol 2018;75:842-9.
PMID: 29610831.</td><td>3</td><td>1130 patients of 0-95 years old (mean 37.4 years) received genotype-guided therapy for carbamazepine-indications for 8 weeks. 79% of patients had epilepsy, 6% schizophrenia, 5% bipolar disorder, and 5% trigeminal neuralgia. 932 patients without HLA-A*3101 were treated with carbamazepine and 197 patients with HLA-A*3101 were treated with an alternative (including among others valproic acid, levetiracetam, zonisamide, phenytoin, clonazepam, lamotrigine, and phenobarbital, either as monotherapy or as combination therapy). 1 patient with HLA-A*3101 was started on carbamazepine, but discontinued this due to other causes than cutaneous adverse events. Telephone interviews of all patients were conducted once weekly to monitor for symptoms of cutaneous adverse drug reactions. In addition, all patients were requested to immediately visit cooperating hospitals or the nearest hospital specializing in dermatology for evaluation of any suspected cutaneous adverse drug reaction symptoms. Only definite or probable cases were defined as carbamazepine-induced cutaneous adverse events. The historical (not genotype-guided) incidence of carbamazepine-induced cutaneous adverse events was estimated from two health care databases. The frequency of HLA-A*3101 carriers in this Japanese population was 17.7%.
For 9 of the HLA-A*3101 carriers (4.5%), neuropsychiatrists could not find suitable alternative drugs.
Relevant co-medication was not excluded.
On the basis of the incidence of carbamazepine-induced cutaneous adverse events obtained from the health care data base showing the smallest incidence (3.4%), it was determined that 1059 patients would provide a statistical power of 80% to detect a reduction in the incidence from 3.4% to 1.5%.

Results:
Incidence of adverse events for HLA-A*3101 carriers on an alternative drug compared to patients without HLA-A*3101 on carbamazepine:
<table><tr><td></td><td></td><td>value for non-carriers</td></tr><tr><td>drug discontinuation due to cutaneous adverse events</td><td>NS</td><td>4.6%</td></tr><tr><td>definite or probable drug-induced cutaneous adverse events</td><td>NS
Of the HLA-B*3101 carriers, 1.5% developed a cutaneous adverse events (induced by zonisamide for 2 patients and sulbactam/penicillin for a 3rd patient). The cutaneous adverse event was either MPE of not diagnosable.</td><td>2.7%</td></tr><tr><td></td><td>For the non-carriers, the cutaneous adverse event was induced by carbamazepine in 23 patients (2.5%), by zonisamide in 1 patient and by lamotrigine in the remaining patient.
None of the non-carriers with a car-</td><td></td></tr></table></td><td>Author’s conclusion:
”Preemptive HLA-A*31:01 genetic screening significantly decreased the incidence of carbamazepine-induced cADRs among Japanese patients, which suggests that it may be warranted in routine clinical practice.“</td></tr>
</table>

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<td>ref. 3, continuation</td>
<td>A*3101-guided therapy: AA#</td>
<td>
<table>
<tr><td></td><td colspan="2">bamazepine-induced cutaneous adverse event, had SJS/TEN. 3 had drug-induced hypersensitivity syndrome (DRESS or otherwise), 9 MPE, 5 erythema multiforme, and in 6 patients the cutaneous adverse event was not diagnosable. 4 patients (2 with drug-induced hypersensitivity syndrome, 1 with MPE, and 1 with erythema multiforme) required hospitalization for treatment. The 2 patients with drug-induced hypersensitivity syndrome and the patient with MPE underwent intravenous steroid pulse therapy, whereas the patient with an erythema multiforme recovered following the discontinuation of carbamazepine treatment.</td></tr>
<tr><td>fever</td><td>NS</td><td>5.3%</td></tr>
<tr><td>sore throat</td><td>trend for a decrease (p = 0.09) (NS)</td><td>6.3%</td></tr>
<tr><td>fatigue</td><td>NS</td><td>18.8%</td></tr>
<tr><td>dizziness</td><td>NS</td><td>8.2%</td></tr>
<tr><td>insomnia</td><td>NS</td><td>5.5%</td></tr>
<tr><td>anorexia</td><td>NS</td><td>5.6%</td></tr>
<tr><td>constipation</td><td>trend for a decrease (p = 0.08) (NS)</td><td>7.1%</td></tr>
<tr><td>diarrhoea</td><td>NS</td><td>3.9%</td></tr>
<tr><td>xerostomia</td><td>NS</td><td>2.8%</td></tr>
<tr><td>nausea</td><td>NS</td><td>5.6%</td></tr>
<tr><td>vomiting</td><td>NS</td><td>2.6%</td></tr>
</table>
<table>
<tr><td colspan="3">Carbamazepine-induced cutaneous adverse events for genotype-guided therapy (incidence 2.0%) compared to historical controls:</td></tr>
<tr><td></td><td></td><td>value for historical control</td></tr>
<tr><td>OR = 0.60 (95% CI: 0.36-1.00, p = 0.048) (S)</td><td>first historical control</td><td>3.4%</td></tr>
<tr><td>OR = 0.39 (95% CI: 0.26-0.59) (S)</td><td>second historical control</td><td>5.1%</td></tr>
<tr><td colspan="3">Note: The incidence of carbamazepine-induced cutaneous adverse events in the patients without HLA-A*3101 in the genotype-guided therapy, i.e. the patients who were exposed to carbamazepine, did not differ from that of the first historical control (NS), but was lower than that of the second historical control (OR = 0.48 (95% CI: 0.31-0.72)) (S). Considering the relatively low incidence of cutaneous adverse events, this suggests the first historical control cohort to be the better comparison.</td></tr>
<tr><td colspan="3">Note: The SJS/TEN incidence of 0% in the genotype-guided therapy did not differ significantly from the SJS/TEN incidence in the first and second historical control (0.23% and 0.05%, respectively) (NS). This is probably due to the power of the study being based on the much higher incidence of all carbamazepine-induced cutaneous adverse events.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 4
Chouchi M et al.
The HLA-B*15:02 polymorphism and Tegretol®-induced serious cutaneous reactions in epilepsy:</td>
<td>3</td>
<td>Meta-analysis of 9 case-control studies in epilepsy patients using no non-antiepileptic drugs with carbamazepine-tolerant patients as controls. Of the total of 148 cases and 781 controls in the studies, only the 91 cases and 42 controls with epilepsy and without non-antiepileptic drugs were included in the meta-analyses. The authors distinguish between SJS-studies (4 studies) and SJS/TEN-</td>
<td>Author’s conclusion:
”Despite the small number of included studies, the results reveal strong evidence</td>
</tr>
</table>

<table>
<tr>
<td>an updated systematic review and meta-analysis.
Rev Neurol (Paris) 2018;174:278-91.
PMID: 29685430.

ref. 4, continuation</td>
<td>B*1502: E</td>
<td>studies (5 studies). 8 of the studies were in Asians, including all 5 SJS/TEN-studies, and the remaining study in diverse ethnicities. 5 of the studies were in Han Chinese, including 3 SJS/TEN-studies.
Of the 9 studies in this meta-analysis, 3 were included in the meta-analysis of Sukasem 2021.
Meta-analyses were performed with a random-effects model in case of high heterogeneity between the studies and with a fixed-effects model in case of low or absent heterogeneity. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised. Quality of the included studies was not assessed.
Publication bias analysis was assessed with funnel plots and Egger’s regression test.

Results:
<table>
<tr><td colspan="3">Association between HLA-B*1502 and SJS and/or SJS/TEN:</td></tr>
<tr><td>outcome</td><td>ethnicity</td><td>OR (95% CI)</td></tr>
<tr><td>all</td><td>all</td><td>27.3 (9.9-75.2) (S)</td></tr>
<tr><td>all</td><td>Han Chinese</td><td>42.1 (9.6-184.5) (S)</td></tr>
<tr><td>SJS</td><td>all</td><td>152.1 (34.7-665.9) (S)</td></tr>
<tr><td>SJS/TEN</td><td>all (= Asian)</td><td>14.0 (7.3-26.9) (S)</td></tr>
<tr><td>SJS/TEN</td><td>Han Chinese</td><td>17.9 (8.4-38.0) (S)</td></tr>
<tr><td colspan="3">Heterogeneity between the studies was significant and high for:
- all outcomes, all ethnicities
- all outcomes, Han Chinese
Heterogeneity between the studies was not-significant and low for:
- SJS, all ethnicities
Heterogeneity between the studies was not-significant and absent for:
- SJS/TEN, all ethnicities (= Asian)
- SJS/TEN, Han Chinese</td></tr>
<tr><td colspan="3">There were indications for publication bias for all comparisons.</td></tr>
</table>
</td>
<td>that the HLA-B*15:02 polymorphism can induce severe cutaneous reactions among Asian carbamazepine users. These findings should prompt physicians to individualize carbamazepine therapy for patients with epilepsy.”</td>
</tr>
<tr>
<td>ref. 5
Wang Q et al. Association between the HLA-B alleles and carbamazepine-induced SJS/TEN: a meta-analysis.
Epilepsy Res 2017;135:19-28.
PMID: 28618376.</td>
<td>4</td>
<td>Meta-analyses of case-control studies with carbamazepine-tolerant or population controls. All studies were in Asians. Only studies with a score ≥ 5 on the 9-item Newcastle-Ottawa scale for study quality were included. All included studies had either a score of 5 or 6 on the Newcastle-Ottawa scale. All of the SJS/TEN patients were diagnosed based on Roujeau’s clinical morphology criteria.
Only HLA-B alleles other than *1502 were analysed.
There were 2 studies with a total of 10 cases and 88 tolerant controls and another 2 studies with a total of 40 cases and 757 population controls for HLA-B*1511.
There were 6 studies with a total of 278 cases and 531 tolerant controls for HLA-B*4001.
There were 3 studies with a total of 103 cases and 202 tolerant controls for HLA-B*4601.
There were 5 studies with a total of 139 cases and 366 tolerant controls for HLA-B*5801. Because there was significant heterogeneity between the studies, the meta-analysis was performed after excluding the study causing this. The remaining 4 studies had a total of 119 cases and 241 controls.
There were 5 studies for HLA-B*5101 and for HLA-B*5502.
There were 3 studies for HLA-B*1301, for HLA-B*3802, for HLA-B*5102, for HLA-B*5401, and for HLA-B*5601.
There were 2 studies for HLA-B*1525 and for HLA-B*3505.
Meta-analyses were performed with a random-effects model in case of significant heterogeneity between the studies and with a fixed-effects model in the absence of</td>
<td>Author’s conclusion:
”Our study demonstrated that in the Asian population, HLA-B*4001, HLA-B*4601, HLA-B *5801 were strong protective factors in the development of carbamazepine-induced SJS/TEN whereas HLA-B *1511 was a risk factor. While more studies may be needed in order to confirm these findings, consideration should be taken into testing Asian patients for at-risk alleles prior to carbamazepine therapy initiation.”</td>
</tr>
</table>

ref. 5, continuation

significant heterogeneity. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardized.
Quality of the included studies was assessed with the Newcastle-Ottawa Scale and only studies with a score ≥ 5 (≥ 56% of the maximum score) were included. Only total scores were reported and not the scores for each criterium. Because the limited number of studies in each meta-analysis, the fail-safe number with significance set at 0.05 ($N_{fs0.05}$) for each meta-analysis was applied to assess the publication bias.

Results:

Association between different HLA-B alleles and SJS/ TEN:	
HLA-B allele	
*1511	OR = 13.9 (95% CI: 4.6-41.7) (S)
	14.0% of the cases and 1.1% of the controls was *1511 carrier.
*4001	OR = 0.22 (95% CI: 0.14-0.35) (S)
	9.4% of the cases and 32.0% of the tolerant controls was *4001 carrier.
	Significance was lost when the 3 Chinese studies were excluded. The authors suggest that this might be due to the study on Japanese patients, which showed a non-significant increase in risk.
*4601	OR = 0.49 (95% CI: 0.25-0.95) (S)
	16.5% of the cases and 25.7% of the tolerant controls was *4601 carrier.
	Significance was lost when either the Han Chinese or the Vietnamese study were excluded. The third study in Thai only found a small effect.
*5801	OR = 0.23 (95% CI: 0.09-0.58) (S)
	4.2% of the cases and 19.5% of the tolerant controls was *5801 carrier.
	Note: The study that was excluded because it caused heterogeneity, found a significant higher risk of SJS/TEN in *5801 carriers. The pooled OR was not significant, when this study was included. This study in North-eastern Han Chinese patients found a low frequency of HLA-B*1502 in carbamazepine-induced SJS cases.
*1301	NS
*1525	NS
*3505	NS
*3802	NS
*5101	NS
*5102	NS
*5401	trend for a decreased risk (p = 0.07) (NS)
*5502	NS
*5601	NS
Heterogeneity between the studies was significant for *3505 and *5101, and for *5801 before exclusion of the 5th study. Heterogeneity between the studies was not significant for the remaining comparisons.	
The fail-safe number values were elevated for *1511 and *4001, suggesting that the associations based on the current data were reliable. However, the fail-safe	

B*1511: E

B*4001: AA#

B*4601: AA#

B*5801: AA#

B*1301: AA

B*1525: AA

B*3505: AA

B*3802: AA

B*5101: AA

B*5102: AA

B*5401: AA

B*5502: AA

B*5601: AA

<table>
<tr><td>ref. 5, continuation</td><td></td><td>number values were not elevated for *4601 and for *5801 if the 5th study was included.</td><td></td></tr>
<tr><td>ref. 6
Genin E et al.
HLA-A*31:01 and different types of carbamazepine-induced severe cutaneous adverse reactions: an international study and meta-analysis.
Pharmacogenomics J 2014;14:281-8.
PubMed PMID: 24322785.</td><td>3

A*3101: E</td><td>Meta-analyses of 8 case-control studies (3 in Europeans and 5 in Asians) with carbamazepine-tolerant patients as controls.
For DRESS, 39 cases and 579 controls in Europeans and 80 cases and 712 controls in Asians were included.
For SJS/TEN, 36 cases and 579 controls in Europeans and 131 cases and 712 controls in Asians were included.
A random effects model was used for the analyses.
A random effects model was used for all meta-analyses, but prospective registration of the protocol was not mentioned. The search and selection strategy and the method of data extraction were not specified.
Quality of the included studies was not assessed.
Publication bias analysis was not performed.

Results:
Association between HLA-A*3101 and cutaneous adverse events:
<table><tr><td>adverse event</td><td>ethnicity</td><td>OR</td><td>95% CI</td></tr><tr><td rowspan="5">DRESS</td><td>All</td><td>13.2 (S)</td><td>8.4-20.8</td></tr><tr><td>European</td><td>24.1 (S)</td><td>9.6-60.3</td></tr><tr><td>Asian</td><td>10.3 (S)</td><td>5.9-17.7</td></tr><tr><td colspan="3">46% of the European cases and 50% of the Asian cases had A*3101.</td></tr><tr><td rowspan="5">SJS/TEN</td><td>All</td><td>3.9 (S)</td><td>1.4-11.5</td></tr><tr><td>European</td><td>7.9 (S)</td><td>2.7-23.6</td></tr><tr><td>Asian</td><td>NS</td><td></td></tr><tr><td colspan="3">22% of the European cases and 8% of the Asian cases had A*3101.</td></tr></table>For DRESS, heterogeneity between the studies was not significant and absent or low.
For SJS/TEN, heterogeneity was not significant and moderate for Europeans, but significant and high for Asians and all ethnicities.

Based on data of a study with 10 European and 10 Chinese DRESS cases and 53 Chinese SJS/TEN cases, the authors calculated the number needed to test to prevent one case of carbamazepine-induced severe cutaneous adverse event (NNT).
Considering an incidence of carbamazepine-induced DRESS of 0.05% in both European and Chinese patients, the NNT for HLA-A*3101 was 3,334 in Europeans and 5,000 in Asians. The number of patients who would be unnecessarily denied carbamazepine was 38 and 41 per 1,000 tested patients respectively. The positive predictive value of HLA-A*3101 was 0.89% in Europeans and 0.59% in Chinese.
Considering an incidence of carbamazepine-induced SJS/TEN in Asians of 0.25%, the NNT for HLA-B*1502 was 527 and the number of patients who would be unnecessarily denied carbamazepine was 53 per 1,000 tested patients. The positive predictive value of HLA-B*1502 was 3.37%.
For testing of both HLA-A*3101 and HLA-B*1502, the NNT in Chinese was 455 and the number of patients who would be unnecessarily denied carbamazepine was 94 per 1,000 tested patients. The positive predictive value of HLA-B*1502 or HLA-A*3101 was 2.26%.</td><td>Author’s conclusion:
”A meta-analysis of this and other published studies confirmed that in all populations, HLA-A*31:01 had an extremely strong association with carbamazepine-DRESS, but a much weaker association with carbamazepine-SJS/TEN. Our data revealed that HLA-A*31:01 is a specific predictor for carbamazepine-DRESS but not for carbamazepine-SJS/TEN.”</td></tr>
<tr><td>ref. 7
Bloch KM et al.
Pharmacogenetics of antiepileptic drug-induced hypersensi-</td><td>3</td><td>Meta-analyses of case-control studies.
For HLA-B*1502 and SJS/TEN, 15 studies in Asians with 251 cases and 832 controls were included.
For HLA-B*1502 and MPE, 4 studies in Han Chinese with 94 cases and 281 controls were included.</td><td>Author’s conclusion:
”Subgroup analyses confirmed a strong association</td></tr>
</table>

<table>
<tr>
<td>tivity.
Pharmacogenomics 2014;15:857-68.
PubMed PMID: 24897291.

ref. 7, continuation</td>
<td>B*1502: E

A*3101: E</td>
<td>For HLA-A*3101 and SJS/TEN, 4 studies in Japanese, Koreans or Europeans with 29 cases and 792 controls were included.
Of the 15 HLA-B*1502 and SJS/TEN studies in this meta-analysis, 5 were included in the meta-analysis of Sukasem 2021, and 4 in the meta-analysis of Chouchi 2018.
All 4 HLA-A*3101 studies in this meta-analysis, were included in the meta-analysis of Genin 2014.
A fixed effects model was used for the analyses, whereas a random effects model should be chosen when presence of heterogeneity cannot be excluded. The search strategy was specified, but the selection strategy and the method of data extraction were not.
Quality of the included studies was not assessed.
Publication bias analysis was not performed.

Results:
<table>
<tr><td colspan="4">Association between HLA-alleles and cutaneous adverse events:</td></tr>
<tr><td>HLA-allele</td><td>adverse event</td><td>OR</td><td>95% CI</td></tr>
<tr><td rowspan="2">B*1502</td><td rowspan="2">SJS/TEN</td><td>79.0 (S)</td><td>47.0-133.0</td></tr>
<tr><td colspan="2">72-100% of the Chinese, Thai or Malaysian cases had B*1502, versus 14% of the Korean cases and 0% of the Japanese cases.</td></tr>
<tr><td>B*1502</td><td>MPE</td><td>NS</td><td></td></tr>
<tr><td rowspan="2">A*3101</td><td rowspan="2">SJS/TEN</td><td>8.0 (S)</td><td>5.6-11.3</td></tr>
<tr><td colspan="2">In studies with more than 5 cases, 42-83% of the cases had A*3101.</td></tr>
<tr><td colspan="4">Heterogeneity between the studies was not significant and low to moderate.</td></tr>
</table>
</td>
<td>between HLA-B*15:02 and carbamazepine-induced SJS/TEN. no association was demonstrated between HLA-B* 15:02 and carbamazepine-induced MPE in the Asian population, confirming that HLA-B*15:02 is a risk factor for SJS/TEN alone in Asian populations.”</td>
</tr>
<tr>
<td>ref. 8
Grover S et al. HLA alleles and hypersensitivity to carbamazepine: an updated systematic review with meta-analysis. Pharmacogenet Genomics 2014;24:94-112.
PubMed PMID: 24336023.</td>
<td>3</td>
<td>Meta-analyses of 20 case-control studies with 720 cases, 1,512 carbamazepine-tolerant controls and 1,113 normal controls.
For HLA-B*1502, SJS/TEN and carbamazepine-tolerant controls, 11 studies in Asians with 205 cases and 692 controls were included. For HLA-B*1502, SJS/TEN and normal controls, 7 studies in Asians with 86 cases and 1,123 controls were included. 4 studies with 41 cases investigated both controls and were included in both meta-analyses.
For HLA-B*1502 and HSS/MPE, 5 Asian studies with 119 cases (of which 106 MPE) and 325 controls were included. All of these studies were also included in the SJS/TEN-analysis.
For HLA-A*3101 and SJS/TEN, 6 studies in Asians or Whites with 105 cases and 968 controls were included. The Asian studies were 2 studies in Chinese, 1 in Japanese and 1 in Koreans.
For HLA-A*3101 and HSS/MPE, 6 studies in Asians or Whites with 273 cases (95 HSS and 178 MPE) and 988 controls were included. 5 of these studies were also included in the SJS/TEN analysis.
6 studies were included for HLA-B*5101 and HLA-B*5801, 5 studies for HLA-B*4001, 3 studies for HLA-A*2402, HLA-B*1301, HLA-B*1501, HLA-B*1511, HLA-B*4601, HLA-B*5502 and HLA-B*5601, and at least 2 independent studies for the other HLA alleles.
For HLA-B*1511 and SJS/TEN, 2 studies in Japanese or Koreans with 10 cases and 83 controls were included.
For HLA-B*5101, 6 studies in Asians with 185 cases (including 84 SJS/TEN (derived from 5 studies), 27 HSS/MPE, 26 HSS) and 643 controls were included.
For HLA-B*4001, 6 studies in Asians with 191 cases (inclu-</td>
<td>Author’s conclusion:
”In summary, our meta-analysis showed the presence of HLA alleles contributing toward risk of as well as protection against various carbamazepine-induced cutaneous adverse drug reactions.”</td>
</tr>
</table>

<table>
<tr>
<td>ref. 8, continuation</td>
<td>B*1502: E</td>
<td>ding 131 SJS/TEN (derived from 4 studies), 48 HSS/MPE, 30 HSS) and 362 controls were included.
For HLA-B*2402, 3 studies in Asians with 176 cases (67 SJS/TEN, 22 HSS and 19 MPE) and 570 controls were included.
For HLA-B*5801 and SJS/TEN, 4 studies in Asians with 77 cases and 218 controls were included.
4 of the 7 HLA-A*3101 studies in this meta-analysis, were included in the meta-analyses of Genin 2014 and Bloch 2014.
All 11 HLA-B*1502 studies in this meta-analysis were included in the meta-analysis of Bloch 2014, 5 in the meta-analysis of Sukasem 2021, and 3 in the meta-analysis of Chouchi 2018.
Both HLA-B*1511 studies in this meta-analysis were included in the meta-analysis of Wang 2017.
2 of the 5 studies on HLA-B*5101 and SJS/TEN in this meta-analysis were included in the meta-analysis of Wang 2017.
3 of the 4 studies on HLA-B*4001 and SJS/TEN in this meta-analysis were included in the meta-analysis of Wang 2017.
1 of the 3 studies on HLA-B*4601 and cutaneous adverse events in this meta-analysis were included in the meta-analysis of Wang 2017.
2 of the 4 studies on HLA-B*5801 in this meta-analysis were included in the meta-analysis of Wang 2017.
1 of the 3 studies on HLA-B*1301 and cutaneous adverse events in this meta-analysis were included in the meta-analysis of Wang 2017.
1 of the 2 studies on HLA-B*3802 and cutaneous adverse events in this meta-analysis were included in the meta-analysis of Wang 2017.
2 of the 3 studies on HLA-B*5502 and cutaneous adverse events in this meta-analysis were included in the meta-analysis of Wang 2017.
2 of the 3 HLA-B*5601 studies in this meta-analysis (all on SJS/TEN) were included in the meta-analysis of Wang 2017.
A random effects model was used when heterogeneity between the studies was considerable. Otherwise, a fixed effects model was used. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardized.
Quality of the included studies was not assessed.
Publication bias was analysed for all comparisons by funnel plot and Egger’s test.

Results:
<table>
<tr><td colspan="4">Association between HLA alleles and cutaneous adverse events:</td></tr>
<tr><td>HLA allele</td><td>adverse event</td><td>OR</td><td>95% CI</td></tr>
<tr><td>B*1502</td><td>SJS/TEN</td><td>80.7 (S)</td><td>45.6-142.8</td></tr>
<tr><td colspan="4">90% of the cases had B*1502. The OR above was in comparison with carbamazepine-tolerant patients. In comparison with normal controls: OR = 45.4 (95% CI: 21.0-98.2) (S). Heterogeneity was lost after exclusion of one of three specific studies (two of the six Chinese studies or the only Korean</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

ref. 8, continuation				study).	
		B*1502	HSS/MPE	trend (NS; OR = 1.84, p = 0.066)	
		B*1502	MPE	1.97 (S)	1.02-3.82
				19% of the cases had B*1502.	
		A*3101	SJS/TEN	5.65 (S)	2.70-11.78
				14% of the cases had A*3101. Heterogeneity disappeared and OR increased (OR = 11.19; 95% CI: 4.69-26.70) after exclusion of the two Chinese studies. Significance was lost after exclusion of the 2 studies in Whites.	
	A*3101: E	A*3101	HSS/MPE	8.58 (S)	5.55-13.28
		A*3101	HSS	10.15 (S)	6.11-16.87
				46% of the cases had A*3101. Significance remained after exclusion of the 2 studies in Whites.	
		A*3101	MPE	7.24 (S)	3.84-13.63
				19% of the cases had A*3101. Significance was lost after exclusion of the 2 studies in Whites.	
	B*1511: E	B*1511	SJS/TEN	17.43 (S)	3.12-97.40
				40% of the cases had B*1511.	
	B*5101: E	B*5101	all	1.71 (S)	1.08-2.69
		B*5101	SJS/TEN	NS	
		B*5101	HSS/MPE	NS	
		B*5101	HSS	NS	
	B*4001: AA[#]	B*4001	all	0.32 (S)	0.19-0.53
		B*4001	SJS/TEN	trend (NS; OR = 0.30, p = 0.051)	
				Exclusion of the Thai and/or Japanese study resulted in a significant OR (for the 2 Chinese studies: OR = 0.14 (S); 95% CI: 0.06-0.32; no heterogeneity).	
		B*4001	HSS/MPE	NS	
		B*4001	HSS	NS	
	A*2402: AA[#]	B*4001	MPE	NS	
		A*2402	SJS/TEN	0.27 (S)	0.11-0.64
		A*2402	HSS/MPE	NS	
	B*5801: AA[#]	A*2402	HSS	NS	
		B*5801	SJS/TEN	0.38 (S)	0.15-0.98
	A*0201: AA A*1101: AA A*3303: AA B*0702: AA B*1301: AA B*1501: AA B*1518: AA B*3802: AA B*4002: AA B*4601: AA B*5502: AA	No significant results were found for the following HLA alleles (NS): A*0201 A*1101 A*3303 B*0702 B*1301 B*1501 B*1518 B*3802 B*4002 B*4601 B*5502 B*5601			
		Heterogeneity between the studies was high for the following comparisons: - B*4001, SJS/TEN - B*2402, HSS/MPE - B*5101, HSS/MPE - B*5101, HSS Heterogeneity between the studies was not significant and moderate for the following comparisons: - B*1502, SJS/TEN, tolerant controls - A*3101, SJS/TEN - B*5101, all cutaneous adverse events - B*5101, SJS/TEN Heterogeneity between the studies was not significant and low for the following comparisons: - B*4001, all cutaneous adverse events			

<table>
<tr>
<td>ref. 8, continuation</td>
<td>B*5601:
AA</td>
<td>
<table>
<tr><td>Heterogeneity between the studies was absent or negligible for the following comparisons:
- B*1502, SJS/TEN, normal controls
- B*1502, HSS/MPE
- B*1502, MPE
- A*3101, HSS/MPE
- A*3101, HSS
- A*3101, MPE
- A*3101, SJS/TEN, White/Korean/Japanese
- B*1511, SJS/TEN
- B*4001, HSS/MPE
- B*4001, HSS
- B*4001, MPE
- B*2402, SJS/TEN
- B*2402, HSS
- B*5801, SJS/TEN</td></tr>
<tr><td>There were no indications for publication bias.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 9
Tangamornsuksan W et al.
Relationship between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis.
JAMA Dermatol 2013;149:1025-32.
PubMed PMID: 23884208.</td>
<td>4

B*1502:
E</td>
<td>Meta-analysis of 11 case-control studies with 175 cases of SJS/TEN and 602 matched carbamazepine-tolerant controls. Of the 11 studies, 5 were in Han-Chinese, 2 in Thai and 1 each in Malaysians, Koreans, Japanese and Whites. After excluding the studies in Whites and Japanese, 170 cases and 526 controls remained.
Meta-analysis of 6 case-control studies with 52 cases of SJS/TEN and 2,949 population controls. Of the 6 studies, 2 were in Japanese and 1 each in Koreans, Indians, Caucasians and a mixed population (Chinese/Indian/Malaysian). One study provided data for both meta-analyses.
All included studies had a score of 4-6 on the 9-item Newcastle-Ottawa scale for study quality.
Of the 16 HLA-B*1502 studies in this meta-analysis, 10 were included in the meta-analyses of Bloch 2014 and Grover 2014, 4 in the meta-analysis of Sukasem 2021, and 2 in the meta-analysis of Chouchi 2018.
The authors did not include the studies of Chung 2004, Ikeda 2010, Wang 2011 and Kulkantrakorn 2012, because some cases in these studies were also in the included studies of Hung 2006, Kaniwa 2008, Shi 2012 and Tassaneeyakul 2010, respectively. The meta-analysis of Sukasem 2021 included both studies of the couples Chung 2014/Hung 2006 and Tassaneeyakul 2010/Kulkantrakorn 2012, and the meta-analyses of Bloch 2014 and Grover 2014 both studies of the couples Wang 2011/Shi 2012 and Tassaneeyakul 2010/Kulkantrakorn 2012.
A random effects model was used for the analyses but prospective registration of the protocol was not mentioned.
The search and selection strategy was transparent and the data extraction was standardised.
Quality of the included studies was assessed with the Newcastle-Ottawa Scale. Only total scores were reported and not the scores for each criterium.
Publication bias was analysed by funnel plot, and Begg's and Egger's test, but only for all ethnicities.

Results:
<table>
<tr><td colspan="4">Association between HLA-B*1502 and SJS/TEN:</td></tr>
<tr><td>Controls</td><td>ethnicity</td><td>OR</td><td>95% CI</td></tr>
<tr><td rowspan="6">carbamazepine-tolerant</td><td>All</td><td>79.8 (S)</td><td>28.5-224.1</td></tr>
<tr><td>Han Chinese</td><td>115.3 (S)</td><td>18.2-732.1</td></tr>
<tr><td>Thai</td><td>54.4 (S)</td><td>16.3-182.0</td></tr>
<tr><td>Malaysian
(1 study)</td><td>221.0 (S)</td><td>3.85-12,694</td></tr>
<tr><td>Korean
(1 study)</td><td>NS</td><td></td></tr>
<tr><td>Whites
(1 study)</td><td>-</td><td></td></tr>
</table>
</td>
<td>Author's conclusion:
"We found a strong relationship between the HLA-B*1502 allele and carbamazepine-induced SJS and TEN in Han-Chinese, Thai, and Malaysian populations."</td>
</tr>
</table>

<table>
<tr><td>ref. 9, continuation</td><td></td><td>
<table>
<tr><td></td><td>Japanese
(1 study)</td><td>-</td><td></td></tr>
<tr><td></td><td colspan="3">The studies in Whites and Japanese were excluded from the meta-analysis, because B*1502 was not detected in these studies (neither in the cases nor in the controls).
72-100% of the Chinese cases, 88-100% of the Thai cases and 100% of the Malaysian cases had B*1502.
Exclusion of a study with Han Chinese from the north and south of China, reduced the heterogeneity for the Chinese sub-group from high to low, and resulted in a similar OR (113.7; 95% CI: 44.2-292.2).</td></tr>
<tr><td rowspan="7">popula-tion

(1 study for each ethnicity)</td><td>All</td><td>57.6 (S)</td><td>12.5-265.1</td></tr>
<tr><td>Chinese/Indi-an/Malaysian</td><td>16.2 (S)</td><td>5.0-52.2</td></tr>
<tr><td>Indian</td><td>54.6 (S)</td><td>2.3-1326.2</td></tr>
<tr><td>European (Whites/Asian/ African)</td><td>644.5 (S)</td><td>64.7-6431.4</td></tr>
<tr><td>Korean</td><td>40.3 (S)</td><td>3.2-265.1</td></tr>
<tr><td>Japanese</td><td>49.4 (S)</td><td>1.6-1531.1</td></tr>
<tr><td colspan="3">One Japanese study was excluded from the meta-analysis, because B*1502 was not detected (neither in the cases nor in the controls).
75% of the Chinese/Indian/Malaysian and Indian cases, 33% of the European cases, 14% of the Korean cases and 0% of the Japanese cases had B*1502.</td></tr>
<tr><td colspan="4">Heterogeneity between the studies was significant and high for carbamazepine-tolerant controls and Chinese and for population controls and all ethnicities.
Heterogeneity between the studies was not significant and moderate for carbamazepine-tolerant controls and all ethnicities.</td></tr>
<tr><td colspan="4">There were no indications for publication bias.</td></tr>
</table>
</td><td></td></tr>
<tr><td>ref. 10
Yip VL et al.
HLA genotype and carbamazepine-induced cutaneous adverse drug reac-tions: a systematic review.
Clin Pharmacol Ther 2012;92:757-65.
PubMed PMID: 23132554.</td><td>3</td><td>Meta-analyses of case-control studies with carbamaze-pine-tolerant controls.
For HLA-B*1502 and SJS/TEN, 9 studies in Asians with 160 cases and 663 controls were included. 5 of the studies were in Han Chinese, 3 in Thai and 1 in Malaysians.
For HLA-B*1502 and HSS/MPE, 6 studies in Asians with 139 cases and 399 controls were included. All of these studies were also included in the SJS/TEN analysis.
For HLA-A*3101 and all cutaneous adverse events, 4 studies in Asians or Whites with 264 cases and 871 controls were included. The Asian studies were 1 each in Chinese, Japanese and Koreans.
All 9 HLA-B*1502 studies in this meta-analysis were inclu-ded in the meta-analysis of Bloch 2014, 8 were included in the meta-analyses of Grover 2014 and Tangamornsuksan 2013, 4 in the meta-analysis of Sukasem 2021, and 2 in the meta-analysis of Chouchi 2018.
All 4 HLA-A*3101 studies in this meta-analysis, were inclu-ded in the meta-analyses of Genin 2014 and Grover 2014, and 3 were included in the meta-analysis of Bloch 2014.
A random effects model was used, but prospective regis-tration of the protocol was not mentioned. The search and selection strategy was transparent and the data extraction was standardised.
Quality of the included studies was evaluated in accordan-ce with criteria for assessment of the quality of pharmaco-genetic studies as set out by Jorgensen and Williamson, but results were not reported.</td><td>Author’s conclu-sion:
”Carriage of HLA-B*1502 in Asian patients was asso-ciated with a poo-led OR of 113.4 for carbamazepine-induced SJS and TEN. A total of 461 patients would need to be scree-ned for HLA-B*1502 to prevent one episode of SJS/TEN. HLA-A*3101 is signifi-cantly associated with all phenoty-pes of carbamaze-pine-hypersensiti-vity in multiple ethnicities with a pooled OR of 9.5. Between 47 and 67 patients would need to be tested for HLA-A*3101 to</td></tr>
</table>

<table>
<tr>
<td>ref. 10, continuation</td>
<td>B*1502: E

A*3101: E</td>
<td>Publication bias analysis was not performed.

Results:
<table>
<tr><td colspan="4">Association between HLA alleles and cutaneous adverse events:</td></tr>
<tr><td>HLA allele</td><td>adverse event</td><td>OR</td><td>95% CI</td></tr>
<tr><td rowspan="2">B*1502</td><td rowspan="2">SJS/TEN</td><td>113.4 (S)</td><td>51.2-251.0</td></tr>
<tr><td colspan="2">96% of the cases had B*1502.</td></tr>
<tr><td>B*1502</td><td>HSS/MPE</td><td>NS</td><td></td></tr>
<tr><td rowspan="2">A*3101</td><td rowspan="2">all</td><td>9.5 (S)</td><td>6.4-13.9</td></tr>
<tr><td colspan="2">39% of the cases had A*3101 (26% of the White cases and 58% of the Japanese cases).</td></tr>
<tr><td colspan="4">Heterogeneity between the studies was not significant and low.</td></tr>
</table>
Based on the data of the meta-analyses of B*1502 and SJS/TEN, and A*3101 and all adverse events, the authors calculated the number needed to test to prevent one case of carbamazepine-induced cutaneous adverse events (NNT).
Considering an incidence of carbamazepine-induced SJS/TEN in Southeast Asians of 0.23%, the NNT for HLA-B*1502 was 461. The positive predictive value of HLA-B*1502 was 1.8%.
Considering an incidence of all carbamazepine-induced cutaneous adverse events of 10% in Whites and 2.9% in Japanese, the NNT for HLA-A*3101 was 47 in Whites and 67 in Japanese. The positive predictive value of HLA-A*3101 was 43% in Whites and 12% in Japanese.</td>
<td>prevent one episode of hypersensitivity.”</td>
</tr>
<tr>
<td>ref. 11
Chen P et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med 2011;364:1126-33. PubMed PMID: 21428768.</td>
<td>3

B*1502-guided therapy: AA#</td>
<td>4,335 patients of 0.6-98.2 years old (mean 56.5 years) received genotype-guided therapy for carbamazepine-indications for 2 months. Neuralgia was the indication in more than 50% of patients, epilepsy in 14% of subjects. 4,120 patients without HLA-B*1502 were treated with carbamazepine and 215 patients with HLA-B*1502 were treated with an alternative (including gabapentin, valproic acid, oxcarbazepine, imipramine, clonazepam, lamotrigine, naproxen and prednisolone). All subjects were counselled about the risk of SJS/TEN and asked to return to the hospital immediately in the event that early symptoms developed. The historical (not genotype-guided) incidence of carbamazepine-induced SJS/TEN was estimated from a health care database. The frequency of HLA-B*1502 carriers in this Taiwanese population was 7.7%. Relevant co-medication was not excluded.

Results:
<table>
<tr><td colspan="3">Incidence of SJS/TEN:</td></tr>
<tr><td>genotype-guided</td><td>0%</td><td rowspan="2">S</td></tr>
<tr><td>not genotype-guided</td><td>0.23%</td></tr>
<tr><td colspan="3">In the genotype-guided therapy, mild cutaneous events developed in 6.0% of patients and severe cutaneous events requiring hospitalisation (maculopapular eruption, hypersensitivity syndrome or urticaria) in 0.16% of patients.</td></tr>
</table>
Note: Based on the decrease in SJS/TEN incidence of 0.23% and the HLA-B*1502 carrier frequency of 7.7%, the positive predictive factor of HLA-B*1502 for development of SJS/TEN is 3.0%.</td>
<td>Author’s conclusion:
”The identification of subjects carrying the HLA-B*1502 allele and the avoidance of carbamazepine therapy in these subjects was strongly associated with a decrease in the incidence of carbamazepine-induced SJS–TEN.“</td>
</tr>
<tr>
<td>ref. 12
SmPC Tegretol (carbamazepine) 14-01-22.</td>
<td>0</td>
<td><u>Dosing</u>:
Before deciding to start treatment and if possible, patients of Han Chinese or Thai ancestry should be screened for HLA-B*1502, because this allele is a strong predictor for</td>
<td></td>
</tr>
</table>

ref. 12, continuation	B*1502: E	the risk of the serious carbamazepine-associated adverse event SJS. Warning: *Cutaneous reactions* Serious and sometimes fatal cutaneous reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported during treatment with carbamazepine. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. Indications about the role of different HLA alleles in predisposing patients to immune-mediated side effects are increasing. These reactions can necessitate hospitalisation and can be life-threatening. Patients starting carbamazepine should be educated in advance about these possible side effects and be carefully monitored for cutaneous reactions. Most cases of SJS and TEN during Tegretol occur in the first months of treatment. When symptoms (for example exacerbating rash, often accompanied with blisters or skin lesions) occur, treatment with carbamazepine should be discontinued immediately and an alternative treatment should be considered. The best results in treatment of SJS and TEN are achieved by early diagnosis and immediate discontinuation of each suspected drug. Early discontinuation is associated with a better prognosis. In patients developing SJS or TEN during Tegretol use, treatment with Tegretol should never be restarted. *HLA-B*1502 allele – in Han Chinese, Thai and other Asian populations* HLA-B*1502 in persons of Han Chinese or Thai ancestry was found to be in strong association with the risk of development of serious cutaneous reactions, known as Stevens-Johnson syndrome (SJS), when treated with carbamazepine. The prevalence of HLA-B*1502-carriers is approximately 2-12% in Han Chinese and approximately 8% in Thai. Before treatment with carbamazepine is started, these persons should be screened for this allele if possible. If the screening assay is positive, carbamazepine should not be used, unless there is no alternative therapy possible. Patients with a negative screening assay for HLA-B*1502 have a low risk of SJS, although the reaction still can occur very rarely. There are some data indicating that the risk of serious carbamazepine-related TEN/SJS is also increased in other Asian populations. Because of the prevalence of this allele in other Asian populations (for instance more than 15% in the Philippines and Malaysia and recently reported allele frequencies of 2% and 6% respectively in Korea and India), one can consider testing patients from risk populations for the presence of HLA-B*1502. The prevalence of the HLA-B*1502 allele is negligibly small in for instance persons of European ancestry, African populations, the investigated Spanish/Latin-American populations and Japanese (<1%). The allele frequency is the percentage of the chromosomes in the indicated population. Every human has two copies of each chromosome and alleles can be inherited. For this reason, the percentage of patients carrying a copy of the allele on one of the two copies of the chromosomes is almost twice the allele frequency. Because carrying an allele on one of the two copies of the chromosomes increases the risk of developing an adverse event, the percentage of patients that is at risk is almost twice the allele	

ref. 12, continuation	A*3101: E	frequency. *HLA-A*3101 allele – European ancestry and Japanese populations* There are some data indicating that HLA-A*3101 in European and Japanese populations is possibly associated with an increased risk of carbamazepine-induced cutaneous adverse events, including SJS, TEN, drug-induced rash with eosinophilia (DRESS) or less serious acute generalised exanthematous pustulosis (AGEP) and maculopapular eruption. The frequency of the HLA-A*3101 allele varies widely between ethnic populations. The HLA-A*3101 allele has a prevalence of 2-5% in European populations and of approximately 10% in the Japanese population. The presence of the HLA-A*3101 allele in persons of European ancestry increases the risk of carbamazepine-induced cutaneous reactions (usually less serious) from 5% in the general population to 26.0%, whereas the absence of this allele decreases the risk from 5% to 3.8%. The allele frequency is the percentage of the chromosomes in the indicated population. Every human has two copies of each chromosome and alleles can be inherited. For this reason, the percentage of patients carrying a copy of the allele on one of the two copies of the chromosomes is almost twice the allele frequency. Because carrying an allele on one of the two copies of the chromosomes increases the risk of developing an adverse event, the percentage of patients that is at risk is almost twice the allele frequency. There is insufficient evidence to recommend screening for the presence of HLA-A*3101 before starting treatment with carbamazepine. If a patient of European or Japanese ancestry is known to be positive for the HLA-A*3101 allele, therapy with carbamazepine can be considered if the expected benefits are larger than the risks. *Hypersensitivity* Tegretol can lead to (systemic) hypersensitivity reactions, including a delayed hypersensitivity disorder involving multiple organs (known as hypersensitivity syndrome or DRESS), resulting in occurrence of different combinations of fever, rash, vasculitis, lymphadenopathy, pseudolymphoma, arthralgia, leukopenia, eosinophilia, hepatosplenomegaly, liver function test abnormalities and vanishing bile duct syndrome (destruction and loss of intrahepatic bile ducts). Other organs can also be affected (for instance lungs, kidneys, pancreas, myocard and colon). The HLA-A*3101 allele is associated with the development of the hypersensitivity syndrome, including maculopapular rash. Patients who developed a hypersensitivity reaction on carbamazepine, should be informed that in approximately 25-30% of these patients cross-reactivity to oxcarbazepine can occur. Cross-reactivity can also occur between carbamazepine and other aromatic antiepileptics (such as phenytoin, primidone and phenobarbital). In general, treatment with Tegretol should be discontinued immediately when hypersensitivity reactions occur. <u>Adverse events</u>: Cutaneous and subcutaneous disorders: Very often: allergic dermatitis, urticaria, which could lead to serious symptoms. Sometimes: dermatitis exfoliativa. Very rare: Stevens-Johnson syndrome*, toxic epidermal necrolysis (TEN or Lyell syndrome)*, erythema multiforme and nodosum, purpura.	

ref. 12, continuation		* In some Asian countries also reported as rare. Frequency unknown: acute generalised exanthematous pustulosis (AGEP). Indications for an association between genetic markers and the development of cutaneous adverse events, such as SJS, TEN, DRESS, AGEP, and maculopapular eruption, are increasing. In Japanese and European patients, an association of these cutaneous adverse events with the use of carbamazepine and presence of the HLA-A*3101 allele is reported. For the marker HLA-B*1502, a strong association with SJS and TEN in people of Han Chinese, Thai and some other Asian ancestry has been shown. Pharmacodynamics: The incidence of SJS is increased very strongly in carriers of the HLA-B*1502 allele. 10 to 15% of all patients with a South-East Asian ancestry (South-China, Taiwan) and 1 to 4% of the population of South and East Asia are carriers of this allele.	
ref. 13 SmPC Tegretol (carbamazepine), USA, 20-03-18.	0 B*1502: E	Boxed warning: *Serious dermatologic reactions and HLA-B*1502 allele* Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported during treatment with Tegretol. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with Tegretol. Patients testing positive for the allele should not be treated with Tegretol unless the benefit clearly out-weighs the risk. Warnings: *Serious dermatologic reactions* Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with Tegretol treatment. The risk of these events is estimated to be about 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. However, the risk in some Asian countries is estimated to be about 10 times higher. Tegretol should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. *SJS/TEN and HLA-B*1502 allele* Retrospective case-control studies have found that in patients of Chinese ancestry there is a strong association between the risk of developing SJS/TEN with carbamazepine treatment and the presence of an inherited variant of the HLA-B gene, HLA-B*1502. The occurrence of higher rates of these reactions in countries with higher frequencies of this allele suggests that the risk may be increased in allele-positive individuals of any ethnicity. Across Asian populations, notable variation exists in the prevalence of HLA-B*1502. Greater than 15% of the population is reported positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of HLA-B*1502, averaging 2% to 4%, but higher in some	

ref. 13, continuation	A*3101: E	groups. HLA-B*1502 is present in less than 1% of the population in Japan and Korea. HLA-B*1502 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans). Prior to initiating Tegretol therapy, testing for HLA-B*1502 should be performed in patients with ancestry in populations in which HLA-B*1502 may be present. In deciding which patients to screen, the rates provided above for the prevalence of HLA-B*1502 may offer a rough guide, keeping in mind the limitations of these figures due to wide variability in rates even within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry. Tegretol should not be used in patients positive for HLA-B*1502 unless the benefits clearly outweigh the risks. Tested patients who are found to be negative for the allele are thought to have a low risk of SJS/TEN. Over 90% of Tegretol treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration in determining the need for screening of genetically at-risk patients currently on Tegretol. The HLA-B*1502 allele has not been found to predict risk of less severe adverse cutaneous reactions from Tegretol such as maculopapular eruption (MPE) or to predict Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Chinese ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable. *Hypersensitivity reactions and HLA-A*3101 allele* Retrospective case-control studies in patients of European, Korean, and Japanese ancestry have found a moderate association between the risk of developing hypersensitivity reactions and the presence of HLA-A*3101, an inherited allelic variant of the HLA-A gene, in patients using carbamazepine. These hypersensitivity reactions include SJS/TEN, maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms (see DRESS/Multi-organ hypersensitivity below). HLA-A*3101 is expected to be carried by more than 15% of patients of Japanese, Native American, Southern Indian (for example, Tamil Nadu) and some Arabic ancestry; up to about 10% in patients of Han Chinese, Korean, European, Latin American, and other Indian ancestry; and up to about 5% in African-Americans and patients of Thai, Taiwanese, and Chinese (Hong Kong) ancestry. The risks and benefits of Tegretol therapy should be weighed before considering Tegretol in patients known to be positive for HLA-A*3101. Application of HLA genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B*1502-positive and HLA-A*3101-positive patients treated with Tegretol will not develop SJS/TEN or other hypersensitivity reactions, and these reactions can still occur infrequently in HLA-B*1502-negative and HLA-A*3101-negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, SJS/TEN and other hypersensitivity reactions, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic	

ref. 13, continuation		monitoring, have not been studied. Precautions: *Laboratory tests* For genetically at-risk patients, high-resolution 'HLA-B*1502 typing' is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected. Adverse reactions: The following additional adverse reactions have been reported: Skin: Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), Acute Generalized Exanthematous Pustulosis (AGEP), pruritic and erythematous rashes, urticaria, exfoliative dermatitis, erythema multiforme and nodosum, purpura, and aggravation of disseminated lupus erythematosus. In certain cases, discontinuation of therapy may be necessary.	

Risk group	-

Comments:

- We only included meta-analyses (for HLA-B*1502 only meta-analyses with more than 15 cases) and comparisons of genotype-guided with not genotype-guided therapy in the risk analysis. Other articles did not contribute enough to the evidence to be included.
  The meta-analysis of Moutaouakkil 2019 (Moutaouakkil Y et al. Diagnostic utility of human leukocyte antigen B*15:02 screening in severe carbamazepine hypersensitivity syndrome. Ann Indian Acad Neurol 2019;22:377-83. PMID: 31736555) was not included, because the meta-analysis for the diagnostic odds ratio included one study twice (with slightly different control groups) (the study of Wang Q et al. Association between HLA-B*1502 allele and carbamazepine-induced severe cutaneous adverse reactions in Han people of Southern China mainland. Seizure 2011;20:446-8).
- Cost-effectiveness:
  QALY = quality-adjusted life-year
  *HLA-B*1502*
  - Yuliwulandari R et al. Cost-effectiveness analysis of genotyping for HLA-B*15:02 in Indonesian patients with epilepsy using a generic model. Pharmacogenomics J 2021;21:476-83. PMID: 33824430.
    For Indonesian patients of 40 years or older with newly diagnosed epilepsy, genotype-guided therapy was not cost-effective compared to carbamazepine for all patients (costs were 656,444,671 Indonesian Rupiah (IDR) per quality-adjusted life-year (QALY) gained, which is higher than the cost-effectiveness threshold of 150,000,000 IDR/QALY used in Indonesia (estimated as three times the gross domestic product per capita)). Genotype-guided therapy consisted of carbamazepine for patients without HLA-B*1502 and valproic acid for patients with HLA-B*1502. The costs per QALY for valproic acid (alternative drug) for all patients was even higher (2,634,975,574 IDR), due to higher costs and the same number of QALY gained. Thus, neither HLA-B*1502 screening nor substitution with valproic acid meets the Indonesian threshold for cost-effectiveness. However, the improved outcomes with this test in other Asian countries may inform the desirability of implementation in Indonesia even with suboptimal cost-effectiveness.
    At a cost-effectiveness threshold of IDR 500,000,000, genotype-guided therapy was more likely to be cost effective than carbamazepine for all and valproic acid for all.
    Evaluation was performed from a healthcare provider/payer perspective. Lifelong direct medical costs were calculated (assuming a mean duration of epilepsy treatment of 30 years). The calculated costs were 21,678,072 IDR for carbamazepine for all patients, 28,629,918 IDR for the genotype-guided therapy and 49,610,785 IDR for valproic acid for all patients. Compared with carbamazepine for all patients, the increase in QALYs was 0.011 for both the genotype-guided therapy and valproic acid for all patients. It was assumed that valproic acid has efficacy and safety profiles comparable with those of carbamazepine, but without the risk of SJS/TEN. It was also assumed that neither carbamazepine nor valproic acid induces other adverse drug reactions, that the probability of valproic acid-induced SJS/TEN is zero, and that the probability of carbamazepine -induced SJS/TEN in an HLA-B*1502 negative population is zero. The probability of carbamazepine-induced SJS/TEN in HLA-B*1502-positive patients in Indonesia was assumed to be 1.1% (Yuliwulandari R et al. Association of the HLA-B alleles with carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in the Javanese and Sundanese population of Indonesia: the important role of the HLA-B75 serotype. Pharmacogenomics 2017;18:1643-8). This was calculated based on the assumption that the incidence of carbamazepine-induced SJS/TEN in the Indonesian population is similar to that reported in other countries, especially in the case of data reported from the Thai population. The prevalence of HLA-B*1502 carriers in the study population was 20.8% (Yuliwulandari R et al. Polymorphisms of HLA genes in Western

Javanese (Indonesia): close affinities to Southeast Asian populations. Tissue Antigens 2009;73:46-53). The calculation was based on a price of carbamazepine treatment of 1,064,909 IDR/year, a price of treatment with valproic acid of 2,457,384 IDR/year, a price of treatment of SJS/TEN of 5,026,302 IDR/year, a price of treatment of SJS/TEN sequelae (dry eye syndrome) of 4,425,000 IDR/year, and genotyping costs of 1,000,000 IDR.
The authors calculated that 423 Indonesian patients need to be tested for the HLA-B*1502 allele to prevent one case of carbamazepine-induced SJS/TEN.

- Zhou Y et al. Global frequencies of clinically important HLA alleles and their implications for the cost-effectiveness of pre-emptive pharmacogenetic testing. Clin Pharmacol Ther 2021;109:160-74. PMID: 32535895.
The authors consolidated HLA genotypes from at least 3.5 million individuals across 66 countries provided by the Allele Frequency Net Database and the Estonian Biobank. and modelled the country-specific cost-effectiveness of genetic testing. They conclude that, for carbamazepine, pre-emptive genotyping of HLA-B*1502 is only cost-effective across most of East and South Asia.
HLA-B*1502 is common throughout South and East Asian populations with the exception of Japan (< 0.1%), ranging from 22% in the Philippines to 1.5% in South Korea. Moreover, HLA-B*1502 is prevalent in Asian communities in the United States (4.1%) and South Africa (3.1%), as well as in the Roma minority in Spain (1%), which originates from North-West India. In contrast, HLA-B*1502 is rare (< 1%) in all analysed non-Asian populations. Based on these data, the authors estimate a total of 483.3 million HLA-B*1502 carriers in South and East Asia corresponding to 1 in 8 individuals. In contrast, only 3 million non-Asian carriers are expected globally.
Less than 130 patients need to be genotyped for HLA-B*1502 to prevent one case of SJS/TEN in the Philippines, Malaysia, Indonesia, Singapore, and China, whereas > 9,000 individuals need to be tested to prevent one case in Europe. Accordingly, pre-emptive genotyping of HLA-B*1502 in patients initiating carbamazepine is likely to be cost-effective across Southern Asia, whereas it is unlikely to be cost-effective in other populations at test costs of $40 per patient. Additionally, pre-emptive genotyping of HLA-B*1502 could become a dominant strategy (i.e. resulting in both better treatment and lower costs) in China and most countries in Southern Asia if their incremental treatment costs are below the calculated corresponding thresholds.
The authors calculated a positive predictive value of HLA-B*1502 for development of SJS/TEN of 5.6%.
In addition, they indicate that recommendations for HLA-B*1502 genotyping remained largely unaffected by an increase in genotyping costs, and that pre-emptive HLA-B*1502 testing in the United States is reimbursed for all patients with Asian ancestry. Finally, the authors indicate that their estimates align with the literature regarding the cost-effectiveness of HLA-B*1502 testing for carbamazepine in South East Asia.
- Choi H et al. Cost-effectiveness of screening for HLA-B*1502 prior to initiation of carbamazepine in epilepsy patients of Asian ancestry in the United States. Epilepsia 2019;60:1472-81. PMID: 31158306.
Compared with carbamazepine for all, HLA-B*1502-guided therapy is cost-effective at a willingness to pay threshold of US$ 50,000/QALY for adult Asian epilepsy patients with a mean age of 39 years in the United States (costs of US$ 27,058 per QALY gained). Genotype guided therapy consisted of carbamazepine for patients without HLA-B*1502 and levetiracetam for patients with HLA-B*1502.
Analysis was from the perspective of the US health care sector. Lifelong direct medical costs and indirect (productivity loss) costs for seizure-free state and persistent seizure state were calculated. For carbamazepine for all patients, the calculated costs were US$ 147,437 and the calculated QALYs 6.28. For the genotype-guided therapy, the calculated costs were US$ 188,949 and the calculated QALYs 7.82. The calculation was based on a price of treatment with controlled-release carbamazepine 600 mg/day of US$ 208/month, a price of treatment with levetiracetam 1500 mg/day of US$ 456/month, costs of SJS, SJS/TEN or TEN of US$ 2,701/month, costs of persistent seizures of US$ 1,540/month, costs of seizure-free state of US$ 355/month, and genotyping costs of US$ 144. The prevalence of HLA-B*1502 carriers in Asians in the USA (5%) was derived from a publication on the FDA recommendation for carbamazepine (Ferrell PB Jr et al. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics 2008;9:1543-6). The probability of occurrence of carbamazepine-induced SJS, overlap SJS/TEN, and TEN for HLA-B*1502-positive patients (10%, occurrence only in month 1 and 2 of exposure), and the mortality rates for carbamazepine-induced SJS (13%), SJS/TEN (27%), and TEN (40%) were derived from previous pharmacoepidemiologic studies (Roujeau JC et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995;333:1600-7; Sekula P et al. Evaluation of SCORTEN on a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis included in the RegiSCAR study. J Burn Care Res 2011;32:237-45; and Kim SH et al. Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. Epilepsy Res 2011;97:190-7). Summary estimates of the sensitivity and specificity of HLA-B*1502 screening (0.91 and 0.90) were based on seven primary studies. The monthly probability of having persistent seizures after continuing 1 month of carbamazepine treatment (0.87) and after continuing 1 month of levetiracetam treatment (0.89), and the monthly rate of discontinuing the medication due to adverse effects other than SJS/TEN for carbamazepine (0.19) and for levetiracetam (0.14), were derived from a prospective, multicentre, double-blind study comparing carbamazepine and levetiracetam for seizure control in newly diagnosed adult epilepsy patients. The probability of mortality was based on age-specific annual mortality rates from US life tables. For additional excess mortality attributable to seizure persistence or recurrence, an average estimate of standardized mortality ratio of 2.33 was used.

By varying the input parameters, the probability of genotype-guided therapy being cost-effective, was calculated to be 99.69%. Although genotype-guided therapy was more expensive than carbamazepine for all, it was more effective, yielding more QALYs, across all Asian ethnic groups.
The parameter that had the largest impact on potential life-years saved was the prevalence rate of the HLA-B*1502 allele in the population. Threshold analysis showed genotype-guided therapy to be not cost-effective in populations with a HLA-B*1502 frequency <0.35%. In all Asian populations mentioned in the article (Japanese not mentioned), the HLA-B*1502 frequency was higher than 0.35% (varying from 0.5% in Koreans to 11.5% in Singaporeans, resulting in additional costs of genotype-guided therapy of US$25,776-46,200/QALY.

- Chong HY et al. Is universal HLA-B*15:02 screening a cost-effective option in an ethnically diverse population? A case study of Malaysia. Br J Dermatol 2017;177:1102-12. PMID: 28346659.
Compared with carbamazepine for all, HLA-B*1502-guided therapy is more expensive and worse (i.e. providing less quality-adjusted life years (QALY)) in ethnically-diverse Malaysians aged 19 years old with newly-diagnosed epilepsy (0.0255 QALYs loss at an additional cost of US$707). The same was true for valproic acid for all (0.2622 QALYs loss at an additional cost of US$4,127). Genotype-guided therapy consisted of carbamazepine for patients without HLA-B*1502 and valproic acid for patients with HLA-B*1502.
As for seizure control, the highest number of patients with 12-month remission was estimated for carbamazepine for all (n=847), followed by genotype-guided therapy (n=833), and valproic acid for all (n=740).
For genotype-guided therapy and valproic acid for all, there was 1 SJS/TEN per 10,000 patients, compared to 46 for carbamazepine for all. The number needed to genotype to prevent one SJS/TEN event was 222.
Calculation was performed from a societal perspective. Lifelong direct medical costs, direct non-medical costs (transportation and additional food expenditure), and indirect costs (productivity loss due to illness) were calculated. Lifelong epilepsy treatment was assumed. The calculation was based on a price of treatment with carbamazepine of US$ 238/year, a price of treatment with valproic acid of US$ 243/year, a price of treatment with topiramate of US$ 1,355/year, a price of treatment of SJS/TEN of US$ 1,876, a price of treatment of the most common late ocular complication of SJS/TEN (severe dry-eye syndrome) of US$ 135/year, and genotyping costs of US$ 59. For the cost of epilepsy management, it was assumed that patients had 3 specialist visits per year, with constant drug costs throughout treatment. The alternative antiepileptic drugs were valproic acid for patients in whom carbamazepine treatment failed or induced SJS/TEN, and topiramate for patients in whom valproic acid treatment failed or induced SJS/TEN. Evidence derived from literature suggests that valproic acid and topiramate are less efficacious as carbamazepine, with 13% and 16% fewer patients achieving 12-month remission with valproic acid and topiramate, respectively. It was assumed that the probability of valproic acid-induced SJS/TEN was similar to carbamazepine-induced SJS/TEN in patients who were HLA-B*1502 negative, while a zero-probability of topiramate-induced SJS/TEN was assumed, as evidence from literature suggests that the incidence of valproic acid-induced SJS/TEN ranges from 021 to 0.5 per 10,000, and no SJS/TEN cases were reported for topiramate. The ethnicity-weighted prevalence of HLA-B*1502 carriers in Malaysia was estimated to be 15% based on a meta-analysis of the respective allele frequency among the three major ethnicities - Malay, Chinese, and Indian. The ethnicity-weighted incidence of carbamazepine-induced SJS/TEN for the general population in Malaysia was estimated to be 0.46% (Dong D et al. Cost-effectiveness of HLA-B*1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore. Neurology 2012;79:1259-67). Using the association between HLA-B*1502 and carbamazepine-induced SJS/TEN in the Malaysian population (OR 221) (Tangamornsuksan W et al. Relationship between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. JAMA dermatology 2013;149:1025-32), the probabilities of carbamazepine-induced SJS/TEN in patients with and without HLA-B*1502 were calculated to be 2.95% and 0.01%, respectively. A 42% increase in mortality (standardized mortality ratio (SMR) 1.42) for newly-diagnosed epilepsy patients and a two-fold increase in mortality (SMR 2.05) for uncontrolled epilepsy patients was derived from literature. It was assumed that there is no increased risk among patients who were in remission.
By varying the input parameters, the probability of carbamazepine for all to be cost-effective at a willingness-to-pay threshold per QALY gained of US$ 8,982 (i.e. the gross domestic product per capita in Malaysia) was calculated to be 96%. The probability of genotype-guided therapy being cost-effective at this threshold was calculated to be only 4%. The hazard ratio of efficacy associated with valproic acid had the greatest potential impact on both additional costs and QALYs gained. while the key driver of the QALYs gained was the probability of carbamazepine-induced SJS/TEN in HLA-B*1502 positive patients.

- Plumpton CO et al. A systematic review of economic evaluations of pharmacogenetic testing for prevention of adverse drug reactions. Pharmacoeconomics 2016;34:771-93. PubMed PMID: 26984520.
The authors performed a systematic literature review of economic evaluations of pharmacogenetic tests of HLA-B*1502 prior to carbamazepine. They conclude that evidence exists to support the cost-effectiveness of genotyping HLA-B*1502 prior to carbamazepine, with the majority of high-quality studies indicating that genotyping was either dominant, cost saving or cost-effective across a variety of populations. However, HLA-B*1502 is particularly prevalent in Asian populations, and whilst testing prior to the use of carbamazepine is cost-effective for these populations, the result may not hold for populations with a low frequency of HLA-B*1502.
Three economic evaluations were retrieved for HLA-B*1502: two conducted in Thailand (Rattanavipapong 2013 and Tiamkao 2013) and one in Singapore (Dong 2012). Tiamkao 2013 was a cost-effectiveness analysis, the others were cost-utility analyses. The quality of reporting in the economic evaluations was high for all studies except Tiamkao 2013. High quality was defined as reporting of more than 85% of items on a 24-item

checklist for economic health evaluations. Dong 2012 did not report the perspective of the cost evaluation, i.e. whether it was from the perspective of the national health payer or from another perspective. Tiamkao 2013 did not mention explicitly a time horizon, did not specify that costs and outcomes were discounted and did not mention sensitivity analysis explicitly. Dong 2012 and Tiamkao 2013 stated that the evidence supporting the effectiveness was retrieved from ”association studies”. Rattanavipapong 2013 stated that the evidence supporting the effectiveness was retrieved from ”meta-analysis”. There is no evidence from random controlled trials to support testing prior to carbamazepine treatment.
Of the two Thai studies, Tiamkao 2013 found testing to be cost saving, but the hypothetical comparator used had no risk of adverse drug reactions, and both cost and effectiveness were assumed equal to carbamazepine (costs of an alternative treatment: Thai baht (THB) 32,522,000/QALY (epilepsy) or THB 35,877,000/QALY (neuropathic pain); $US1 = THB30.72; testing: THB 986 saving/patient). The unrealistic scenario of an alternative drug having zero incidence of adverse drug reactions may bias towards pharmacogenetic testing. The other two studies, against realistic comparator drugs, found genotyping to be cost-effective in the base case (Dong 2012: Testing vs. carbamazepine/phenytoin: $US 29,750/QALY; testing dominates valproate; Rattanavipapong 2013: Testing vs. carbamazepine: THB 222,000/QALY (epilepsy) or 130,000/QALY (neuropathic pain); $US1 = TBH30.48). However, cost-effectiveness was sensitive to the prevalence of HLA-B*1502; whilst cost-effective for Singapore Chinese and Malays, genotyping was not cost-effective for Singapore Indians (Dong 2012).
Genetic testing for HLA-B*1502 prior to the use of carbamazepine is an FDA requirement and is recommended by the Canadian regulatory authorities. Testing is routine in Taiwan, with the genotyping fee being covered by national health insurance.

- Rattanavipapong W et al. Economic evaluation of HLA-B*15:02 screening for carbamazepine-induced severe adverse drug reactions in Thailand. Epilepsia 2013;54:1628-38. PubMed PMID: 23895569.
For Thai patients of 20 years or older with neuropathic pain, a HLA-B*1502 genotype-guided therapy was almost more cost-effective than carbamazepine for all patients (costs were 130,000 Thai Baht (THB) per quality-adjusted life-year (QALY) gained, which is comparable to the threshold of 120,000 THB/QALY, which is approximately 4,000 US$/QALY). For epilepsy patients, the HLA-B*1502 genotype-guided therapy was less cost-effective than carbamazepine for all patients (costs were 222,000 THB per QALY gained). However, the incidence of carbamazepine-induced SJS/TEN and the positive predictive value are major factors that influence the cost-effectiveness of HLA-B*1502 screening. Therefore, an active surveillance system to make a more accurate assessment of the incidence of carbamazepine-induced SJS/TEN in the Thai population would enhance the generalisability of the results. Genotype guided therapy consisted of carbamazepine for patients without HLA-B*1502 and either valproic acid (epilepsy) or gabapentin (neuropathic pain) for patients with HLA-B*1502. Genotype guided therapy for epilepsy patients would become cost-effective if the costs for valproic acid would decrease with 44%. With a ceiling threshold of 1,000,000 THB/QALY (approximately 33,350 US$/QALY), the probability of genotype guided therapy being cost-effective would be 84% for both epilepsy patients and patients with neuropathic pain.
Genotype guided therapy was more cost-effective than alternative therapy for all patients (costs were 32,522,000 THB lower per QALY gained for epilepsy patients and 35,877,000 THB lower per QALY gained for patients with neuropathic pain).
Economic evaluation was performed from a societal perspective. Evaluations were performed separately for epilepsy patients and patients with neuropathic pain. Lifelong direct medical and direct non-medical costs were calculated. The treatment period was 2 years for neuropathic pain and lifelong for epilepsy. For epilepsy patients, the calculated costs were 42,000 THB for carbamazepine for all patients, 50,000 THB for the genotype guided therapy and 84,000 THB for valproic acid for all patients. Compared with carbamazepine for all patients, the increase in QALYs was 0.0368 for the genotype-guided therapy and 0.0379 for valproic acid for all patients. For patients with neuropathic pain, the calculated costs were 19,000 THB for carbamazepine for all patients, 23,000 THB for the genotype-guided therapy and 36,000 THB for gabapentin for all patients. Compared with carbamazepine for all patients, the increase in QALYs was 0.0316 for the genotype-guided therapy and 0.0319 for gabapentin for all patients. The calculation was based on a price of carbamazepine treatment of 4,094 THB/year for epilepsy patients and 5,387 THB/year for patients with neuropathic pain, a price of treatment with valproic acid of 15,477 THB/year, a price of treatment with gabapentin of 14,576 THB/year, a price of treatment of SJS/TEN of 25,666-26,970 THB/year and genotyping costs of 1,000 THB. The incidence rate of carbamazepine-induced SJS/TEN in the Thai population (0.27%), the positive predictive value (1.92%) and negative predictive value (99.96%) of HLA-B*1502 screening were derived from a Thai study (Tassaneeyakul W. et al. Association between HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population. Epilepsia 2010;51:926–930). The probability of other adverse drug reactions was derived from a database of the Thai regulatory authorities. Costs and health-related quality of life data were collected from 15 cases with carbamazepine-induced SJS/TEN (5 of whom had epilepsy) and 18 matched controls (5 of whom had epilepsy).
When genotype guided therapy is compared with carbamazepine for all patients, the number of life years saved and QALYs gained is insignificant for patients with both epilepsy and neuropathic pain, reflecting the fact that SJS/TEN is a rare condition. A similar finding is observed when comparing genotype-guided therapy with alternative drugs for all patients.
By varying the input parameters, the probability of genotype-guided therapy being cost-effective at the Thai ceiling ratio of 120,000 THB/QALY gained for epilepsy and neuropathic pain, was calculated to be 16% and 32%, respectively. These percentages were increased at higher ceiling thresholds, at higher incidences of

carbamazepine-induced SJS/TEN, at higher incidences of other carbamazepine-induced side effects, and at shorter treatment durations. For epilepsy patients, these percentages were also increased when the costs for valproic acid were reduced. Genotype-guided therapy for epilepsy patients would become cost-effective if the costs of a 500 mg tablet of valproic acid would decrease from 12.66 THB to 7.07 THB. The costs for HLA-B*1502 screening and other costs did not affect the cost-effectivity. With a ceiling threshold of 1,000,000 THB/QALY (approximately 33,350 US$/QALY), the probability of genotype-guided therapy being cost-effective would be 84% for both epilepsy patients and patients with neuropathic pain.
Carbamazepine is the primary treatment choice for patients with epilepsy and neuropathic pain according to current Thai clinical practice guidelines.
The authors calculated that 343 Thai patients need to be tested for the HLA-B*1502 allele to prevent one case of carbamazepine-induced SJS/TEN.
It was estimated that genotype-guided therapy can reduce the incidence of SJS/TEN with 88% (from 187 patients per year to approximately 23 patients per year).

- Tiamkao S et al. Cost minimization of HLA-B*1502 screening before prescribing carbamazepine in Thailand. Int J Clin Pharm 2013;35:608-12. PubMed PMID: 23649893.
  For Thai patients, the costs of screening of HLA-B*1502 prior to carbamazepine treatment were less than the costs for treatment of SJS/TEN cases if screening was not performed. Per patient, 985.50 Thai Baht (THB) would be saved. This corresponds to approximately 33 US$.
  Data on the allele frequency of HLA-B*1502 in Thai (8.4%), the incidence of SJS/TEN in patients with HLA-B*1502 (88.1%) (Tassaneeyakul W et al. Association between HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population. Epilepsia 2010;51:926–30.) and in patients without HLA-B*1502 (0%) (Chen P et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Eng J Med 2011;364:1126–33.) were retrieved from literature. The costs for treatment of SJS/ TEN were retrieved from the hospital database.
- Dong D et al. Cost-effectiveness of HLA-B*1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore. Neurology 2012;79:1259-67. PubMed PMID: 22955130.
  Compared with carbamazepine for all, HLA-B*1502-guided therapy is cost-effective at a willingness to pay threshold of U$ 50,000/QALY for adult Singaporean Chinese and Malaysian epilepsy patients (costs US$ 37,030/quality-adjusted life year (QALY) gained and US$ 7,930/QALY, respectively), but not for adult Singaporean Indian epilepsy patients (costs US$ 136,630/QALY). For the total Singaporean population, it is cost-effective (costs US$ 29,750/QALY). Population frequency of HLA-B*1502 (mean 14.9% in Singapore; approximately 14% in Chinese, 29% in Malaysians and 4% in Indians), positive predictive value, duration of treatment relative to life expectancy, and costs of alternative drugs were the key drivers influencing cost-effectiveness. Cost-effectiveness is lost if treatment with antiepileptic drugs is lifelong.
  Genotype guided therapy consisted of carbamazepine or phenytoin for patients without HLA-B*1502 and valproic acid for patients with HLA-B*1502.
  Valproic acid treatment for all patients was more expensive and did not provide more QALYs than genotype guided treatment.
  Lifelong direct medical costs were calculated for a period of 30 years. The treatment period was 7 years. For carbamazepine/phenytoin for all patients, the calculated costs were US$ 4,110 and the calculated QALYs 18.846. For the genotype-guided therapy, the calculated costs were US$ 4,680 and the calculated QALYs 18.865. For valproic acid for all patients, the calculated costs were US$ 6,780 and the calculated QALYs 18.865. The calculation was based on a price of treatment with carbamazepine or phenytoin of US$ 170/ year, a price of treatment with valproic acid of US$ 470/year, a price of treatment of SJS, SJS/TEN or TEN of respectively US$ 3,480, US$ 10,250 and US$ 17,030, and genotyping costs of US$ 270. The incidence rate of carbamazepine/phenytoin-induced SJS/TEN in Singapore Chinese was assumed to be the same as the reported incidence rate of carbamazepine-induced SJS/TEN in Taiwan Chinese (0.23%) (Chen P et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med 2011;364:1126 - 33). The relative incidences in different Singaporean ethnicities were estimated based on a voluntary reporting registry of adverse drug reactions of the Singapore Health Sciences Authority. Based on these relative incidences, an incidence of 0.61% and 0.14% was calculated for carbamazepine/phenytoin-induced SJS/ TEN in Singaporean Malaysians and Indians respectively. With the sensitivity and specificity values of Chen 2011, positive predictive values for SJS/TEN development in HLA-B*1502 carriers were calculated to be 5.1% for Singaporean Chinese, 12.5% for Singaporean Malays, and 3.2% for Singaporean Indians. The mean incidence rate and positive predictive value in Singapore were 0.27% and 5.96% respectively.
  By varying the input parameters, the probability of genotype guided therapy being cost-effective, was calculated to be 75%. With a willingness to pay threshold of US$ 31,000/QALY, the probability of genotype-guided therapy being cost-effective, would be more than 50%. However, if treatment is lifelong, genotype-guided therapy would not be cost-effective, regardless of the remaining life expectancy. With a positive predictive value lower than 3.8% or an HLA-B*1502 frequency less than 6.1%, genotype-guided therapy would not be cost-effective. However, lower genotyping cost could compensate for a lower positive predictive value.

*HLA-A*3101*

- Zhou Y et al. Global frequencies of clinically important HLA alleles and their implications for the cost-effectiveness of pre-emptive pharmacogenetic testing. Clin Pharmacol Ther 2021;109:160-74. PMID: 32535895.
  The authors consolidated HLA genotypes from at least 3.5 million individuals across 66 countries provided by the Allele Frequency Net Database and the Estonian Biobank. and modelled the country-specific cost-effec-

tiveness of genetic testing. They conclude that, for carbamazepine, HLA-A*3101 testing is likely to be cost-effective globally.
HLA-A*3101 is prevalent globally. Based on genotype information from 3,578,482 individuals, this allele is most frequent in indigenous populations of the Americas, particularly in Argentina (28.8%), Mexico (10.1%), the United States (7.8%), Nicaragua (6.7%), and Chile (6.6%). Further allele hotspots are Japan (8.5%) and South Korea (5.6%). Populations in which HLA-A*3101 is rare include Ghana (0.4%), Peru (0.5%), and Maori in New Zealand (0.5%). Across Europe allele frequencies range between < 1% in Albania and 5.9% in Sweden. Only limited information was available for African populations. However, the available data from Ghana (0.4%), Uganda (0.9%), Sao Tome and Principe (1.5%), and Tunisia (1.6%), as well as for African Americans (1.1%) suggests that the prevalence of HLA-A*3101 in Africa is overall low. Due to the relatively low predictive power of HLA-A*3101 genotyping, the NNT to prevent one severe cutaneous adverse event exceed 1,000 individuals in most countries with the exception of Japan (NNT = 493.9), South Korea (NNT = 734.9), Sweden (NNT = 703.9), Chile (NNT = 626.7), and indigenous populations in the Americas.
The authors conclude that pre-emptive genotyping of HLA-A*3101 was likely cost-effective globally, primarily due to the substantial gain in QALY upon switching therapy to alternative anticonvulsants in HLA-A*3101 carriers. However, genotype-guided carbamazepine prescribing was not found to be both better and cheaper, indicating that cost effectiveness depends on the cost effectiveness thresholds of the countries.
The authors calculated a positive predictive value of HLA-A*3101 for development of severe cutaneous adverse events of 1.3%. In addition, they indicate that recommendations for HLA-A*3101 genotyping remained largely unaffected by an increase in genotyping costs. Finally, they indicate that their estimates align with the literature regarding the cost-effectiveness of HLA-A*3101 testing for carbamazepine in the United Kingdom.

- Plumpton CO et al. Cost-effectiveness of panel tests for multiple pharmacogenes associated with adverse drug reactions: an evaluation framework. Clin Pharmacol Ther 2019;105:1429-38. PMID: 30466189.
  Based on a stratified analysis and compared with no testing, initial use of a pharmacogenetic panel tests, including HLA-A*3101, HLA-B*1502, HLA-B*5701, HLA-B*5801, HLA-B (158T), and HLA-DQB1 (126Q) was cost-effective in patients eligible for carbamazepine based on HLA-A*3101 testing, but not based on HLA-B*1502 testing. Cost-effectiveness was determined for the United Kingdom.
  Compared with carbamazepine for all, the reported additional, total cost of HLA-A*3101 genotype-guided therapy is £300, inclusive of a test cost of £54, and the quality-adjusted life year (QALY) gained is 0.0234 (Plumpton 2015). These values were included in the calculation, after inflating the additional cost, excluding the cost of testing to 2017 GBP, resulting in a cost of £268. In addition, pharmacogenetic panel test costs of £50 were included.
  For a patient with epilepsy and eligible for carbamazepine or phenytoin (with the incidental findings for all other HLA-alleles), the panel had an additional costs of £15,638 (US $20,330) per QALY gained and would be considered cost-effective with a probability of 0.75 at a threshold of £30,000 per QALY.
  In the case that the panel was to be implemented such that all findings are acted upon (where applicable) regardless of cost-effectiveness, the panel resulted in a cost saving of £378 (US $491) and 0.0069 QALYs gained, therefore, being both better and cheaper than standard care. The probability of cost-effectiveness at the £30,000 per QALY threshold was 1.0 indicating that this panel configuration is cost-effective and should be adopted into routine practice. However, cost-effectiveness can be further improved by removing HLA-B*1502 and not using the panel as a predictive test in patients presenting with gout who are eligible for allopurinol (cost saving of £1,388 (US $1,805) and a QALY gain of 0.0163).
  Alternative drugs were considered to be as effective as the drugs avoided.
- Plumpton CO et al. A systematic review of economic evaluations of pharmacogenetic testing for prevention of adverse drug reactions. Pharmacoeconomics 2016;34:771-93. PubMed PMID: 26984520.
  The authors performed a systematic literature review of economic evaluations of pharmacogenetic tests of HLA-A*3101 prior to carbamazepine. They conclude that the economic evidence for HLA-A*3101 testing prior to using carbamazepine is weak, being based on a single study, but suggests it is cost-effective.
  Only one economic evaluation was retrieved for HLA-A*3101 (Plumpton 2015, UK), which was a cost-utility analysis. The quality of reporting in the economic evaluation was high. High quality was defined as reporting of more than 85% of items on a 24-item checklist for economic health evaluations. The economic evaluation stated that the evidence supporting the effectiveness was retrieved from ”association studies”. There is no evidence from random controlled trials to support testing prior to carbamazepine treatment.
  The economic evaluation found that genotyping prior to prescribing carbamazepine was cost-effective for patients with newly diagnosed epilepsy (£ 12,808/QALY gained and £ 37,314/adverse drug reaction averted; $US1 = £0.62; standard care dominates with respect to life-years gained).
  The clinical recommendation group of the Canadian Pharmacogenomics Network for Drug Safety recommends that carbamazepine should not be prescribed for patients who have not been prescribed carbamazepine previously and who carry at least one HLA-A*3101 allele.
- Plumpton CO et al. Cost-effectiveness of screening for HLA-A*31:01 prior to initiation of carbamazepine in epilepsy. Epilepsia 2015;56:556-63. PubMed PMID: 26046144.
  For carbamazepine-naive 38-year-old epileptic males with 12 seizures per year, HLA-A*3101 genotype-guided therapy was cost-effective when compared with carbamazepine for all patients (£12,808 per QALY gained; cost-effectiveness threshold of £20,000/QALY).
  Testing reduced the expected rate of cutaneous adverse event from 7.8% to 7.0% of patients. The costs per cutaneous adverse event avoided were £37,314.

Genotype-guided therapy consisted of carbamazepine for patients without HLA-A*3101 and lamotrigine for patients with HLA-A*3101. The anti-epileptic drug was changed to valproic acid for patients who developed cutaneous adverse event.

Economic evaluation was performed from the perspective of the National Health Service. Lifelong direct medical costs were calculated. For carbamazepine for all patients, the calculated costs were £ 10,508 and the calculated QALYs 15.7510. For the genotype-guided therapy, the calculated costs were £ 10,808 and the calculated QALYs 15.7744. Clinical data, HLA-A*3101 frequency and costs of treatment of HSS and SJS/TEN were derived from literature and the National Institute of Health and Care Excellence. Costs for treatment of MPE were considered to be equal to the costs of changing the anti-epileptic drug. Pharmacogenetic data were derived from an European study (McCormack M et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med 2011;364:1134-43). The calculation was based on a price of carbamazepine treatment of £1,449.33/year, a price of treatment with lamotrigine of £2,678.48/year, a price of treatment with valproic acid of £1,314.44/year, a price of treatment of mild rash of £821.00, a price of treatment of HSS of £10,676.55, a price of treatment of acute SJS/TEN of £29,737.59, a price of long-term treatment of SJS/TEN of £162.00 and genotyping costs of £51.71 (HLA-A*31-negative patients) or £142.11 (HLA-A*31-positive patients) (mean genotyping costs: £54.26).

The probability of testing being cost-effective at a threshold of £20,000 per QALY was 0.80, but the results were sensitive to estimated remission rates for alternative anti-epileptic drugs. Univariately, the efficacies, utilities, and costs associated with each anti-epileptic drug were the main drivers of cost-effectiveness. The cost-effectiveness of genotype-guided therapy depends on the choice of alternative anti-epileptic drugs and the order in which anti-epileptic drugs are prescribed. In a scenario where the average cost of genotyping is reduced from £54.26 to £10, genotype-guided therapy is more cost-effective (costs of £10,920/QALY compared with carbamazepine for all patients). The number needed to screen to prevent one case of cutaneous adverse events is 125, or 3,667 to prevent one case of HSS or SJS/TEN.

- Existing guidelines:
  - Leckband SG et al. Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and carbamazepine dosing. Clin Pharmacol Ther 2013;94:324-8. PubMed PMID: 23695185 and Phillips EJ et al. Clinical Pharmacogenetics Implementation Consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 update. Clin Pharmacol Ther 2018;103:574-81. PMID: 29392710.

    CPIC indicates that HLA-B*1502 is strongly associated with greater risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in patients treated with carbamazepine. In addition, CPIC indicates that HLA-A*3101 is associated with greater risk of maculopapular exanthema, drug reaction with eosinophilia and systemic symptoms, and SJS/TEN in patients treated with carbamazepine.

    CPIC indicates that there is substantial evidence linking HLA-B*1502 with the risk of SJS/TEN. As references they mention the separate studies, most of which have been integrated in the meta-analyses summarised in our risk analysis. They indicate that the level of evidence provided by these studies for an association between HLA-B*1502 and carbamazepine-induced SJS/TEN is high. They indicate that an increased risk of SJS/TEN has been associated with HLA-B*1502 in Han Chinese (Chung 2004, Hung 2006 and Man 2007) and other Asian groups. Consistent with the regional and ethnic distribution of HLA-B*1502, studies have shown the genetic risk of carbamazepine-associated SJS/TEN to be higher in several Asian countries, including Vietnam (Lonjou 2006), Cambodia (Lonjou 2006), the Reunion Islands (Lonjou 2006), Thailand (Locharernkul 2008 and Tassaneeyakul 2010), some parts of India (specifically Hindus) (Mehta 2009), Malaysia (Chang 2011) and Hong Kong (Man 2007). In the Han Chinese population, the sensitivity of HLA-B*1502 as a predictive test for SJS/TEN has been estimated at 98% and specificity has been estimated at 97%; the positive predictive value is estimated at 7.7% and the negative predictive value is estimated at 100% (Hung 2006). HLA-B*1502 has not been observed in cases of SJS/TEN in various ancestral groups such as Japanese and Korean populations or non-Asian descendants in Europe or North America (Lonjou 2006, Alfirevic 2006, Lonjou 2008, Kaniwa 2008 and Kim 2011). However, it is important to note that in one study, in a group of individuals thought to be of European origin, 4 of 12 individuals with SJS/TEN carried the HLA-B*1502 allele (Lonjou 2008). Subsequently, they were found to have some Asian ancestry. CPIC indicates that this example underscores the importance of considering HLA-B*1502 carrier status regardless of self-reported ethnicity. CPIC also indicates that the FDA label for carbamazepine carries a boxed warning about the risk of SJS/TEN with the presence of the HLA-B*1502 allele and states that patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk. Regardless of ancestry or age of the individual, CPIC indicates that if a patient is carbamazepine-naïve and HLA-B*1502 positive, carbamazepine should be avoided due to the greater risk of SJS/TEN. CPIC classifies this recommendation as strong, indicating that the evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

    Carbamazepine-induced SJS/TEN usually develops within the first 3 months of therapy; therefore, patients who have been taking carbamazepine for longer than 3 months without developing cutaneous reactions are at low risk (but not zero) of carbamazepine-induced adverse events in the future, regardless of HLA-B*1502 status (Roujeau 1995 and Tennis 1997). CPIC recommends to cautiously consider use of carbamazepine if a HLA-B*1502-positive patient has previously used carbamazepine for longer than 3 months without incidence of cutaneous adverse reactions. CPIC classifies this recommendation as optional, indicating that the desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.

CPIC indicates that oxcarbazepine should be avoided in HLA-B*1502 positive oxcarbazepine-naïve patients. Other aromatic anticonvulsants, including eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital, have very limited evidence, if any, linking SJS/TEN with the HLA-B*1502 allele; however, caution should still be used when choosing an alternative agent. CPIC classifies the recommendation for oxcarbazepine as strong and does not classify the recommendation for the other aromatic anticonvulsants.
CPIC indicates that HLA-A*3101 is associated with carbamazepine hypersensitivity reactions, including MPE, DRESS, and SJS/TEN, in many different populations (Yip 2012, included in our risk analysis), with the data strongest for DRESS and SJS/TEN in European and Japanese populations, where the allele frequency is higher. In addition, they indicate that in Southeast Asian populations, the strong association between HLA-B*1502 and carbamazepine-induced SJS/TEN would overwhelm any potential association between HLA-A*3101 and carbamazepine-induced SJS/TEN. In European, African, and Japanese populations where the carriage rate of HLA-B*1502 is less than 1%, HLA-A*3101 appears to be the primary driver of carbamazepine-induced SJS/TEN and other hypersensitivity reactions. HLA-A*3101 is also a risk factor for MPE and DRESS in Han Chinese populations. CPIC indicates that the positive predictive value and number needed to test to prevent one case of all carbamazepine-induced hypersensitivity reactions (most influenced by MPE ⋙ DRESS) combined are most favourable for European populations, and they are estimated at 43% and 47, respectively (Yip VL et al. The HLA-A*3101 allele: influence on carbamazepine treatment. Pharmgenomics Pers Med 2017;10:29-38). As references CPIC mentions the separate studies, most of which have been integrated in the meta-analyses summarised in our risk analysis. CPIC indicates that the level of evidence provided by these studies for an association between HLA-A*3101 and carbamazepine-induced DRESS and SJS/TEN is high, whereas the level of evidence provided for an association between HLA-A*3101 and carbamazepine-induced MPE is moderate. CPIC indicates that if a patient is carbamazepine-naïve and HLA-A*3101 positive, and if alternative agents are available, carbamazepine should be avoided due to the greater risk of SJS/TEN, DRESS, and MPE. CPIC classifies this recommendation as strong. Other aromatic anticonvulsants, including oxcarbazepine, have very limited evidence, if any, linking SJS/TEN, DRESS, and/or MPE with the HLA-A*3101 allele, and thus no recommendation can be made with respect to choosing another aromatic anticonvulsant as an alternative agent. If alternative agents are not available, CPIC indicates that the use of carbamazepine with increased frequency of clinical monitoring can be considered. Therapy should be discontinued at first evidence of a cutaneous adverse reaction. CPIC classifies this recommendation as optional. As previously mentioned, since the latency period for cutaneous adverse drug reactions is known, if the patient is HLA-A*3101 positive and has previously used carbamazepine for longer than three months without incidence of a cutaneous adverse reaction, use of carbamazepine can be cautiously considered. CPIC classifies this recommendation as optional.
CPIC indicates that HLA-B*1502 is the most common HLA-B75 serotype allele in Southeast Asia. Other less frequently carried members of the HLA-B75 serotype include HLA-B*1508, HLA-B*1511, and HLA-B*1521. The HLA proteins coded by these alleles share structural similarity and peptide binding grooves, and hence peptide binding specificities, with HLA-B*1502 and have also been reported in association with carbamazepine-induced SJS/TEN (Kim SH et al. Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. Epilepsy Res 2011; Kaniwa N et al. HLA-B*1511 is a risk factor for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. Epilepsia 2010;51: 2461-5; Shi YW et al. Association between HLA and Stevens-Johnson syndrome induced by carbamazepine in Southern Han Chinese: genetic markers besides B*1502? Basic Clin Pharmacol Toxicol 2012;111:58-64; and Jaruthamsophon K et al. HLA-B*15:21 and carbamazepine-induced Stevens-Johnson syndrome: pooled-data and in silico analysis. Sci Rep 2017;7:45553). Currently the majority of available data focuses on the risk of carbamazepine-induced SJS/TEN conferred by the presence of HLA-B*1502. However, possibility of carbamazepine-induced SJS/TEN with HLA-B*1508, HLA-B*1511, HLA-B*1521, and even less common HLA-B75 serotype alleles such as HLA-B*1530 and HLA-B*1531 where carbamazepine-induced SJS/TEN has yet to be described, needs to be considered a potential risk in patients with these alleles.
CPIC mentions potential benefits and risks of HLA-B*1502 and HLA-A*3101 testing. A potential benefit is a significant reduction in the incidence of serious, sometimes fatal, cutaneous adverse reactions to carbamazepine by identifying those who are at significant risk and using alternative therapy. The success of HLA-B*1502 prospective screening in reducing the rate of SJS/TEN has been demonstrated clinically in a Chinese population (Chen 2011, included in our risk analysis). A potential risk of HLA-B*1502 or HLA-A*3101 testing is ruling out the use of carbamazepine and oxcarbazepine in patients who may not ever develop a hypersensitivity reaction to these drugs. This risk is mitigated by the fact that there are often alternatives to carbamazepine or oxcarbazepine with comparable effectiveness; however, consideration must be given to the risk of cutaneous adverse reactions with other anticonvulsants. For example, it has been demonstrated in an Asian population that a HLA-B*1502 screening policy for carbamazepine will not decrease the overall rate of SJS/TEN if other anticonvulsants associated with SJS/TEN (e.g., phenytoin) are used instead of carbamazepine (Chen Z et al. Effects of a HLA-B*15:02 screening policy on antiepileptic drug use and severe skin reactions. Neurology 2014;83:2077-84). Furthermore, other anticonvulsants may be associated with more unfavourable adverse effect profiles compared to carbamazepine or oxcarbazepine.
Because extensive ethnic admixture has occurred globally and not all carbamazepine- and oxcarbazepine-induced cutaneous adverse reactions can be attributed to HLA-B*1502 or HLA-A*3101, clinicians should carefully monitor all patients as standard practice.
CPIC provides the following recommendations for HLA-B*1502 and/or HLA-A*3101 positive patients:

Genotype[a]	Therapeutic recommendation	Classification of recommendation	Considerations for other aromatic anticonvulsants
HLA-A*3101 positive and HLA-B*1502 negative	- If patient is carbamazepine-naïve and alternative agents are available, do not use carbamazepine. - If patient is carbamazepine-naïve and alternative agents are not available, consider the use of carbamazepine with increased frequency of clinical monitoring. Discontinue therapy at first evidence of a cutaneous adverse reaction. - The latency period for cutaneous adverse drug reactions is variable depending on phenotype; however, all usually occur within three months of regular dosing. Therefore, if the patient has previously used carbamazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine.	Strong Optional Optional	Other aromatic anticonvulsants[c] have very limited evidence, if any, linking SJS/TEN, DRESS, and/or MPE with the HLA-A*3101 allele, and thus no recommendation can be made with respect to choosing another aromatic anticonvulsant as an alternative agent. N/A Previous tolerance of carbamazepine is not indicative of tolerance to other aromatic anticonvulsants.[c]
HLA-B*1502 positive[b] and any HLA-A*3101 genotype (or HLA-A*3101 genotype unknown)	- If patient is carbamazepine-naïve, do not use carbamazepine. - if patient has previously used carbamazepine for longer than 3 months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine	Strong Optional	Other aromatic anticonvulsants[c] have weaker evidence linking SJS/TEN with the HLA-B*1502 allele; however, caution should still be used in choosing an alternative agent.

[a]If only HLA-B*1502 was tested, assume HLA-A*3101 is negative and vice versa.
[b]In addition to HLA-B*1502, risk for carbamazepine-induced SJS/TEN has been reported in association with the most common B75 serotype alleles in Southeast Asia, HLA-B*1508, HLA-B*1511, and HLA-B*1521. Although not described, the possibility of carbamazepine-induced SJS/TEN in association with less frequently carried B75 serotype alleles, such as HLA-B*1530 and HLA-B*1531, should also be considered.
[c]Aromatic anticonvulsants include carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital.

No updates on the published 2017 update were reported on the CPIC-site on 7-3-2022.

- Amstutz U et al. Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. Epilepsia 2014;55:496-506. PMID: 24597466.

The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) concludes that patients carrying HLA-B*1502 are at strongly increased risk for carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) in populations where HLA-B*1502 is common, but not carbamazepine-induced hypersensitivity syndrome (HSS) or maculopapular exanthema (MPE). HLA-B*1502–positive patients with carbamazepine-SJS/TEN have been reported from Asian countries only, including China, Thailand, Malaysia, and India. HLA-B*1502 is rare among Caucasians or Japanese; no HLA-B*1502-positive patients with carbamazepine-SJS/TEN have been reported so far in these groups. HLA-A*3101-positive patients are at increased risk for carbamazepine-induced HSS and MPE, and possibly SJS/TEN and acute generalized exanthematous pustulosis (AGEP). This association has been shown in Caucasian, Japanese, Korean, Chinese, and patients of mixed origin; however, HLA-A*3101 is common in most ethnic groups. Not all patients carrying either risk variant develop an hypersensitivity reaction, resulting in a relatively low positive predictive value of the genetic tests.

CPNDS indicates that there is substantial evidence linking HLA-B*1502 with the risk of SJS/TEN. As referen-

ces they mention the separate studies, most of which have been integrated in the meta-analyses summarised in our risk analysis, and the meta-analysis of Yip 2012, that is included in our risk analysis. They indicate that the level of evidence provided by these studies for an increased risk in carriers of HLA-B*1502 to develop carbamazepine-induced SJS/TEN is strong (++++ evidence). From the literature they deduce a sensitivity of the genetic test for HLA-B*1502 of 80-97% in populations where HLA-B*1502 is common, but a PPV of only 1-5%.
CPNDS indicates that there is evidence linking HLA-A*3101 with the risk of DRESS, MPE, SJS/TEN and acute generalized exanthematous pustulosis (AGEP). As references they mention the separate studies, most of which have been integrated in the meta-analyses summarised in our risk analysis. They indicate that the evidence provided by these studies for an association between HLA-A*3101 and carbamazepine-induced DRESS and MPE is consistent, although with a smaller magnitude of effect compared to HLA-B*1502 and with somewhat limited generalizability because of the smaller number of available studies (+++ evidence). They grade the overall strength of evidence for an association of HLA-A*3101 with carbamazepine-SJS/TEN as low but encouraging (++ evidence), due to significant inconsistency in findings and the small number of cases in individual studies, making it likely that conclusions drawn from the evidence will change based on future research. They indicate that it is difficult to draw any conclusions regarding an association of HLA-A*3101 with carbamazepine-induced AGEP, because HLA-A*3101 has been studied in only two patients with carbamazepine-induced AGEP in the retrieved articles (++ evidence). They indicate, that due to the variability in the effect size reported between different studies, there is some uncertainty about the sensitivity of the genetic test for HLA-A*3101, with estimates ranging from 26% to 61%. Accordingly, there is also uncertainty about the PPV of this test (12-42%). For serious adverse cutaneous events (DRESS and SJS/TEN), CPNDS indicates a PPV of <2%.
CPNDS reports that three studies in populations where HLA-B*1511 is present (Japanese, Korean, and Thai), suggest that HLA-B*1511 increases the risk of SJS/TEN. However, they indicate that further research is needed to strengthen the evidence for an association of HLA-B*1511 with carbamazepine-induced SJS/TEN.
CPNDS provides the following recommendations for HLA-B*1502- and/or HLA-A*3101-positive patients:

Genotype	Therapeutic recommendation	Classification of recommendation	Considerations for other alternatives
HLA-B*1502- or HLA-A*3101-positive	- Alternative medications should be used as first-line therapy. - Consideration in the choice of alternative medications should be given to the possibility of cross-reactivity with structurally similar antiepileptic drugs (oxcarbazepine, lamotrigine, phenytoin, phenobarbital, primidone).	Level A (strong)	The first choice should be given to alternative medications that are structurally different from carbamazepine (level A (strong) recommendation). If structurally different medications are not effective or not tolerated, aromatic antiepileptic drugs other than carbamazepine or oxcarbazepine should be used. Despite a risk of cross-reactivity for these medications, the risk of a severe hypersensitivity reaction appears to be lower than for carbamazepine or oxcarbazepine (level B (moderate) recommendation). Carbamazepine and oxcarbazepine should be used only as a last resort, if all alternative medications prove ineffective or are not tolerated by the patient, or if no alternative medications are available (level C (optional) recommendation). If carbamazepine or oxcarbazepine is administered to a patient who is positive for HLA-B*1502 or HLA-A*3101, strongly increased alertness to the first symptoms of a hypersensitivity reaction is warranted. Patients should therefore be asked to immediately discontinue carbamazepine and consult their treating physician upon the occurrence of a rash or fever. Based on two studies with a total of four SJS/TEN cases, there is suggestive evidence for a similar association of HLA-B*1502 with SJS/TEN for oxcarbazepine as for carbamazepine (++ evidence). On the other hand, the incidence of oxcarbazepine-induced SJS/TEN has been estimated to be 30-40 fold lower compared to carbamazepine in Taiwan Han Chinese patients, suggesting a difference in the risk of SJS/TEN between the two drugs. Therefore, there is currently insufficient evidence to provide a strong recommendation regarding the administration of oxcarbazepine to patients carrying carbamazepine hypersensitivity risk variants. However, given the observation of several cases of oxcarbazepine-induced SJS/TEN in HLA-B*1502-positive patients, avoiding oxcarbazepine as a first-line therapy in such patients may be the safest approach until further evidence is available (level C (optional) recommendation).

			Associations of HLA-B*1502 with SJS/TEN have also been reported for phenytoin and lamotrigine. However, the strength of the reported associations was moderate, with only 8 (31%) of 26 patients with phenytoin-induced SJS/TEN, and 5 (26%) of 19 patients with lamotrigine-induced SJS/TEN carrying HLA-B*1502. Current evidence therefore suggests an increased risk for SJS/TEN for patients who are positive for HLA-B*1502 also when taking phenytoin or lamotrigine; however, the associated risk appears to be lower compared to carbamazepine (++ evidence). Only one study so far has investigated HLA-A*3101 in the context of phenytoin-induced (42 MPE, 3 HSS, one SJS) and lamotrigine-induced (40 MPE, 4 HSS) hypersensitivity reactions. The frequency of HLA-A*3101 compared to tolerant controls was not increased, suggesting that there is no association of this risk variant with phenytoin or lamotrigine hypersensitivity reactions of the same magnitude as observed for carbamazepine.

CPNDS provides the following recommendations for HLA-B*1502 and/or HLA-A*3101 genotyping prior to start of carbamazepine:

Recommendation	Classification of recommendation	Rationale for the recommendation
- Genetic testing for HLA-B*1502 is recommended for all carbamazepine-naive patients before initiation of carbamazepine therapy	Level A (strong) in patients originating from populations where HLA-B*1502 is common, its frequency unknown or whose origin is unknown Level C (optional in patients originating from populations where HLA-B*1502 is rare).	Although the PPVs of the genetic tests are relatively low, the severity of SJS/TEN and DRESS justifies a recommendation for genetic testing because equally effective alternative treatments are available. For HLA-B*1502, the strength of the reported associations combined with the severity of SJS/TEN and the availability of equally effective alternative medications warrants a strong recommendation for testing despite the lower PPV compared to the abacavir HLA-B*5701 test.
- Genetic testing for HLA-A*3101 is recommended for all carbamazepine-naive patients before initiation of carbamazepine therapy	Level B (moderate) in all patients.	For HLA-A*3101 the level of strength of the recommendation is reduced due to the smaller number of studies available compared to HLA-B*1502, the uncertainties related to sensitivity and PPV, and the lack of a prospective evaluation of the potential of the genetic test to reduce hypersensitivity reactions in the retrieved articles.
- In patients who have previously taken carbamazepine for > 3 months without any adverse effects, and in whom reinitiation of carbamazepine is considered, genetic testing is NOT recommended.	Level B (moderate).	The onset of symptoms for carbamazepine-induced hypersensitivity reactions is usually within the first 3 months of therapy. In patients who have previously taken carbamazepine for a duration of >3 months without experiencing any adverse reaction, a hypersensitivity reactions is therefore unlikely to occur upon reinitiation of carbamazepine.
- In patients who have previously taken carbamazepine for a shorter period, genetic testing should be considered.	Level B (moderate).	
In patients who have previously experienced a hypersensitivity reaction potentially related to carbamazepine, genetic testing is recommended as part of the differential diagnosis and for the direction of future therapy.	Level B (moderate).	In patients with a history of a hypersensitivity reaction, for which carbamazepine is a possible culprit drug, a positive test results for HLA-B*1502 or HLA-A*3101 increases the likelihood of the previous hypersensitivity reaction being related to carbamazepine. Genetic testing is therefore recommended as part of the differential diagnosis to assist in the causality assessment of the hypersensitivity reaction, in the context of other possible culprit drugs or other etiologies (e.g., infections). Furthermore, the risk of a severe hypersensitivity reac-

		tion upon readministration of carbamazepine is likely to be strongly increased in patients who previously experienced a hypersensitivity reaction while taking carbamazepine and test positive for HLA-B*1502 or HLA-A*3101. Therefore, genetic testing is particularly recommended in such patients if reinitiation of carbamazepine is considered.
In patients for whom no alternative treatment options are available, genetic testing is recommended to ensure increased alertness to hypersensitivity symptoms in positive patients.	Level B (moderate).	Early discontinuation of the culprit drug has been shown to reduce the risk of mortality associated with severe drug hypersensitivity reactions. Knowledge of a patient's increased risk of hypersensitivity is therefore valuable even if no alternative treatment options are available to ensure increased alertness and monitoring for symptoms of hypersensitivity reactions, allowing for rapid discontinuations of carbamazepine if a hypersensitivity reaction occurs.

- Müller DJ et al. [Pharmacogenetics in psychiatry: state of the art]. Nervenarzt 2018;89:290-9. PMID: 29383410.
  The Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN) supports the recommendations to determine the HLA-B*1502 genotype in patients of Asian origin before using carbamazepine.

Date of the literature search: 4 January 2022.

	Genotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
KNMP Pharmacogenetics Working Group decision	HLA-B*1502	4 E	yes	yes	23 May 2022
	HLA-A*3101	3 E	yes	yes	
	HLA-B*1511	4 E	yes	yes	

Mechanism:
Although the mechanism of hypersensitivity for carbamazepine is not exactly known, experimental data suggests the mechanism described below.
A cellular immune reaction against tissue cells is induced if peptides derived from proteins within these tissue cells bind to specific HLA proteins, are transported to the cell surface and are ”recognised” as foreign by specific immune cell proteins (T-cell receptors). Carbamazepine binds to either the cellular proteins or derived peptides, to specific HLA proteins or to specific T-cell receptors, thus inducing an interaction between an HLA peptide complex and a T-cell receptor, resulting in a cellular immune reaction against tissue cells.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	**Possible Score**	**Given Score**			
		B*1502 Han Chinese or Thai	**B*1502 other, non-Japanese, Asian**	**A*3101**	**B*1511 Han Chinese, Korean,**

					Thai or Japanese
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)					
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	+	+	+	+
• CTCAE Grade 5 (clinical effect score F)	++				
Level of evidence supporting the associated clinical effect grade ≥ 3					
• One study with level of evidence score ≥ 3	+				
• Two studies with level of evidence score ≥ 3	++				+++
• Three or more studies with level of evidence score ≥ 3	+++	+++	+++	+++	
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3					
• 100 < NNG ≤ 1000	+	+	+		
• 10 < NNG ≤ 100	++				
• NNG ≤ 10	+++				
PGx information in the Summary of Product Characteristics (SmPC)					
• At least one genotype/phenotype mentioned	+		+	+	
OR					
• Recommendation to genotype	++	++			
OR					
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++				
Total Score:	10+	7+	6+	5+	4+
Corresponding Clinical Implication Score:		Essential	Essential	Beneficial	Beneficial
Score after taking additional considerations into account:		Beneficial	Beneficial		