HLA: allopurinol 6391

95% CI = 95% confidence interval, DRESS = drug reaction with eosinophilia and systemic symptoms, also known as hypersensitivity syndrome (HSS), EEM = erythema exudativum multiforme, eGFR = estimated glomerular filtration rate, HLA = human leukocyte antigen, HSS = hypersensitivity syndrome, including DRESS, MPE = maculopapular exanthema, NS = not significant, OR = odds ratio, PPV = positive predictive value, 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, the health care professional should consider the next best option.

Brief summary and justification of choices:
Allopurinol can induce the life-threatening cutaneous adverse events SJS/TEN and DRESS. In addition, allopurinol can induce the mild cutaneous adverse event maculopapular exanthema. The hypersensitivity reactions develop in general within two months after the start of allopurinol.
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*5801
HLA-B*5801 is present at a frequency of less than 1% in Northwest-Europeans and Japanese. Its frequency is usually around 5-10% in other East-Asian countries.
Four meta-analyses showed that this allele strongly increased the risk for allopurinol-induced SJS/TEN (OR = 57-106 and OR of having HLA-B*5801 for a case compared to a control = 84-151) (Yu 2017, Wu 2016, Ng 2016, and Somkrua 2011). Two meta-analysis showed the same for all severe cutaneous adverse events (OR = 73-165) (Wu 2016 and Zineh 2011) and another for DRESS (OR = 54) (Ng 2016). In addition, two meta-analyses showed the same in the European subgroup for SJS/TEN (both 3 studies with population controls and one also 1 study with allopurinol-tolerant controls, OR = 44-58 and OR of having HLA-B*5801 for a case compared to a control = 58) (Yu 2017 and Wu 2016) and one for all severe cutaneous adverse events (3 studies, OR = 39-65) (Wu 2016). In addition, three studies in East-Asians showed that excluding HLA-B*5801 positive patients from therapy with allopurinol or starting with an allopurinol tolerance induction protocol for these patients, resulted in reduction of the incidence of allopurinol-induced severe cutaneous adverse events from 0.3% (non-selected patients) or 0.9% or 2.0% (patients with chronic renal insufficiency) to 0% (Park 2019, Jung 2015, Ko 2015).
For this reason, the KNMP Pharmacogenetics Working Group concluded that action is needed for this gene-drug interaction (yes/yes-interaction).
HLA-A*3303, HLA-C*0302 and a six SNP HLA haplotype
Studies investigating an association between HLA-A*3303, HLA-C*0302 and a six SNP HLA haplotype and allopurinol-induced cutaneous adverse events are not included in the risk analysis, because these associations most probably result from a linkage disequilibrium of these HLA-alleles/haplotype with HLA-B*5801 (see 'Comments' below the table with article summaries).
If effects of HLA-alleles are not independent, inclusion of the allele-allopurinol combinations in the electronic decision support systems and/or the KNMP Kennisbank does not result in an improvement of allopurinol therapy.
HLA-B*4601
One study in the risk analysis showed a protective effect of HLA-B*4601 on development of allopurinol-induced severe cutaneous adverse events. However, the study did not find a consistent effect. With allopurinol-tolerant controls, the protective effect was not significant after Bonferroni correction. In addition, this allele was one of the most prevalent alleles and the decrease of its frequency in cases might also be a secondary result of the increase of the frequency of HLA-B*5801. Finally, because the effect is positive, no action is needed.
For these reasons, the KNMP Pharmacogenetics Working Group decided that there was not enough cause for inclusion of this gene-drug combinations in the electronic decision support systems and/or the KNMP Kennisbank.
HLA-DR9, HLA-DR14 and HLA-B48
One study in this risk analysis suggested that HLA-DR9, HLA-DR14 and HLA-B48 increased the risk for allopurinol-induced MPE. However, the study did not find a consistent effect. For none of the alleles was the OR significant with both allopurinol-tolerant and population controls. In addition, none of the ORs would have been significant if Bonferroni correction for multiple comparisons would have been applied. Finally, MPE is a mild and often self-limiting adverse event, so the need for a priori adjustment of allopurinol therapy in case of an increased risk for MPE is low.

For these reasons, 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*4001, HLA-B*3501, HLA-B*1502, HLA-B*1301, HLA-B*5101, HLA-B*3901, HLA-B*3701, HLA-B*2704, HLA-B*5502, HLA-B*1518, HLA-B*3802, HLA-B*3503, HLA-B*4002, HLA-B*4403, HLA-B*5102, HLA-B*5201, HLA-B*5501, HLA-B*5601, HLA-B*6701 and HLA-Cw8

One study in this risk analysis found no effect of these alleles on the risk of allopurinol-induced cutaneous adverse events. Therefore, it was 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*5801: allopurinol, detailed information*

For the included interaction between allopurinol and HLA-B*5801, you can find an overview of the effects in the background information text of the interaction on the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

The justification for the therapeutic recommendations for this genotype you will find below.

Therapeutic recommendation

For the whole group of HLA-B*5801 carriers, the positive predictive value for development of allopurinol-induced severe cutaneous adverse events was 1.6% to 2.0% (Chen 2015 and Ko 2015). For patients with chronic kidney insufficiency this was 8-18% (Park 2019 and Jung 2015). Because of these relatively high positive predictive values and the relatively high fatality of allopurinol-induced severe cutaneous adverse events of 11% (Saksit 2017 and Ng 2016), the recommendation for all patients is to choose an alternative or to precede treatment with allopurinol tolerance induction. Because febuxostat is not associated with an increase of adverse events in HLA-B*5801 carriers (Jung 2015, Ko 2015 and Chohan S. Safety and efficacy of febuxostat treatment in subjects with gout and severe allopurinol adverse reactions. J Rheumatol 2011;38:1957-9), febuxostat is mentioned as a possible alternative.

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

The KNMP Pharmacogenetics Working Group considers genotyping of patients before starting allopurinol to be beneficial for drug safety. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection.

The clinical implication of the gene-drug interaction scores 6 out of the maximum of 10 points for all Dutch patients, and 8 out of the maximum of 10 points for patients of Asian, other than Japanese, or African 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 this score, because there is no equivalent alternative for allopurinol and the positive predictive value of HLA-B*5801 for severe cutaneous adverse events is low. Of the two mentioned alternatives in the therapeutic recommendation for HLA-B*5801 carriers, according to its SmPC febuxostat should be avoided in patients with pre-existing major cardiovascular diseases (e.g. myocardial infarction, stroke or unstable angina). Because cardiovascular diseases are highly prevalent in gout patients, this limits the applicability of febuxostat. The applicability of the second mentioned alternative, induction of tolerance to allopurinol, is strongly hampered by the commercial unavailability of the required low and very low dose formulations of allopurinol. Because the positive predictive value of HLA-B*5801 carriage for development of allopurinol-induced severe cutaneous adverse events is low (1.6-2.0% in the total patient population and 8-18% in patients with chronic kidney insufficiency), a large majority of HLA-B*5801 carriers will be falsely denied allopurinol. So, pre-emptive genotyping will not only diminish severe adverse events, but will also strongly increase the number of patients who are falsely denied the preferred treatment for gout. For this reason, the KNMP Pharmacogenetics Working decided that genotyping for HLA-B*5801 in patients planned to be started on allopurinol is not essential and downgraded the recommendation to beneficial.

The rationale for the (sub)scores on the clinical implication score is indicated below:

HLA-B*5801 has been shown to increase the risk of the severe allopurinol-induced cutaneous adverse events SJS/TEN and DRESS, that result in a mortality rate of 11% (code F corresponding to CTCAE grade 5). This results in the maximum score of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (2 points for code F (CTCAE grade 5)).

Five meta-analyses (with a maximum of 21 studies per meta-analysis) showed that HLA-B*5801 increased the risk of allopurinol-induced severe cutaneous adverse events. 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*5801 positive patients from therapy with allopurinol resulted in reduction of the incidence of severe cutaneous adverse events from 0.3% to 0% (Ko 2015). This corresponds to a number needed to genotype of 333 to avoid one severe cutaneous adverse event in this Han-Chinese population with a HLA-B*5801 carrier frequency of 20%. For many other Asian populations other than Japanese (Korean, Thai, Vietnamese, Malaysian, and Indian), the HLA-B*5801 carrier frequency is approximately 12%, which would amount to a number needed to genotype of 556. In most African countries and in African-Americans, the HLA-B*5801 carrier frequency is higher than 7%, which would amount to a number needed to genotype smaller than 952. In the Netherlands, the HLA-B*5801 carrier frequency is 1,2%, which would amount to a number needed to genotype to avoid one severe cutaneous adverse event of 5556. Two studies in Korean patients with chronic renal insufficiency showed that excluding HLA-B*5801 positive patients from therapy with allopurinol or starting with an allopurinol tolerance induction protocol for these patients, resulted in reduction of the incidence of severe cutaneous adverse events from 0.9% or 2.0% to 0% (Park 2019 and Jung 2015). The reduction from 0.9% to 0% found in the more recent study and based on an almost 9 times higher number of controls, corresponds to a number needed to genotype of 111 to avoid one seve-

re cutaneous adverse event in this population with a HLA-B*5801 carrier frequency of 12.2%. Because of the HLA-B*5801 carrier frequency of 1.2% in the Netherlands, this corresponds to a number needed to genotype to avoid one severe cutaneous adverse event of 1111 in Dutch patients with chronic kidney disease. Because the number needed to genotype to prevent 1 adverse event code ≥ D (grade ≥ 3) is larger than 1000 in Dutch patients (both in all patients and in patients with chronic kidney disease), 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). However, the number needed to genotype in patients of Asian, other than Japanese, or African descent of 111-952 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 mentions that the HLA-B*5801 allele has been demonstrated to be associated with the risk of development of allopurinol related hypersensitivity syndrome and SJS/TEN. In addition, the SmPC indicates that In patient subgroups known to have a high HLA-B*5801 prevalence, screening for this allele should be considered before start of allopurinol treatment (specifically mentioning Han-Chinese, Thai and Koreans). For Dutch patients in general, 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). For patients of Asian, not Japanese, 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).
While the clinical implication score is beneficial for Dutch patients in general, all 3 cost-effectiveness analyses investigating (also) low HLA-B*5801 carrier frequencies suggested genotyping to be not cost-effective (Zhou 2020, Plumpton 2017, and Jutkowitz 2017). In addition, 4 out of 10 cost-effectiveness analyses investigating (also) high HLA-B*5801 carrier frequencies suggested genotyping to be not cost-effective (Pruis 2020, Teng 2020, Chong 2018, and Dong 2015), whereas the other 6 suggested genotyping to be cost-effective (Zhou 2020, Plumpton 2017, Ke 2017, Jutkowitz 2017, Park 2015, and Saokaew 2014). Some cost-effectiveness analyses found the relative effective-ness of allopurinol and the alternative used in HLA-B*5801 carriers in lowering serum uric acid to the target level, so the alternative and maximum allopurinol dose used, to have a strong influence on the cost-effectiveness of genotype-guided therapy. However, especially the older cost-effectiveness analyses did not include the effectiveness difference in their calculations.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr>
<td>ref. 1
Park HW et al.
Efficacy of the HLA-B*58:01 screening test in preventing allopurinol-induced severe cutaneous adverse reactions in patients with chronic renal insufficiency-a prospective study.
J Allergy Clin Immunol Pract 2019;7:1271-6.
PMID: 30580048.</td>
<td>3

genotype</td>
<td>489 patients with chronic renal insufficiency received genotype guided allopurinol therapy for 90 days. 451 patients without HLA-B*5801 were treated with allopurinol, 38 patients with HLA-B*5801 were treated with febuxostat.
Dosing was according to renal function for both allopurinol (50 mg/day, 100 mg/day or more) and febuxostat (40 mg/day, 80 mg/day or more). If early symptoms of severe cutaneous adverse reactions developed, the patients were asked to return to the clinic immediately for a thorough evaluation by allergy specialists. The historical (not genotype guided) incidence of allopurinol-induced severe cutaneous adverse events was determined in 4002 patients with chronic renal insufficiency from the same hospitals who were prescribed allopurinol for more than 3 months over 5 years before start of the genotype guided study. Patients in the historical control were more often female, younger, had higher estimated glomerular filtration rates, and more often used the smallest allopurinol dose of 50 mg/day.
The frequency of HLA-B*5801 carriers in the Korean population was reported to be 12.2%, but was only 7.2% in this Korean genotype guided group.
Relevant comedication was not excluded.
To detect a reduction in the incidence rate from 2.19% (based on the reported HLA-B*5801 carrier frequency in the Korean population and the observed incidence rate of 18% of allopurinol-induced severe cutaneous adverse reactions in HLA-B*58:01-positive patients with chronic renal insufficiency) to 0.219%, 475 patients would provide a power of 80%.

Results:
<table>
<tr><td colspan="2">Incidence of severe cutaneous adverse events compared to the not genotype guided historical control:</td></tr>
<tr><td>genotype guided treatment</td><td>incidence</td></tr>
</table>
</td>
<td>Author's conclusion:
'The present study demonstrated the clinical usefulness of the HLA-B*58:01 screening test before allopurinol administration to prevent allopurinol-induced severe cutaneous adverse reactions in patients with chronic renal insufficiency.'</td>
</tr>
</table>

ref. 1, continuation	guided therapy: AA[#]	<table><tr><td></td><td>in controls</td></tr><tr><td>x 0.0 (S)</td><td>0.95%</td></tr><tr><td colspan="2">In the genotype guided group, 14 patients developed a mild skin rash and 3 itching (all HLA-B*5801-negative). Allopurinol was stopped in these patients. In addition, 1 patient developed hair loss and 1 dizziness on allopurinol.</td></tr><tr><td colspan="2">In the historical controls, 66% of the severe cutaneous adverse events was DRESS, 24% SJS, 5% SJS/TEN overlap, and 5% TEN.</td></tr><tr><td colspan="2">The incidence in controls would correspond to a maximum positive predictive value of HLA-B*5801 carriership for severe cutaneous adverse events of 13% (calculated with the HLA-B*5801 population frequency of 7.2% observed in this study) or 8% (calculated with the HLA-B*5801 population frequency of 12.2% observed in Thai previously) .</td></tr></table> The authors indicate that the costs of genotyping in this study were considerably lower than the costs of treatment of the avoided number of severe cutaneous adverse events. The total costs of genotyping were US$ 50 per patient, so US$ 24,450 for 489 patients. The total health care cost for the management of a patient with severe cutaneous adverse reactions was reported to be approximately US$ 10,300 in Korea. This would corresponds to total costs of US$ 41,200-51,500 for the 4-5 severe cutaneous adverse reactions avoided by the genotype guided therapy in these patients based on the incidence of 0.95% observed in the historical controls.	
ref. 2 Yu KH et al. Diagnostic utility of HLA-B*5801 screening in severe allopurinol hypersensitivity syndrome: an updated systematic review and meta-analysis. Int J Rheum Dis 2017;20:1057-71. PMID: 28857441.	3	Meta-analyses of 11 case-control studies. Population controls were used in 9 case-control studies with a total 162 patients with allopurinol-induced SJS/TEN and 7372 controls. Matched allopurinol-tolerant controls were used in 6 studies with a total of 130 patients with allopurinol-induced SJS/TEN and 414 controls. Because 4 studies used both types of controls, 90 patients with allopurinol-induced SJS/TEN were included in both comparisons, so the total number of patients with allopurinol-induced SJS/TEN in the case-control studies was 202. 3 of the case-control studies were performed in Europeans (all with population controls), 2 in Japanese (all with population controls), and 4 in Han Chinese (3 with population controls), 1 in Koreans and 1 in Thai. The area under the summary receiver operating characteristic curve (the sensitivity-(1-specificity) curve) is a measure of the value of HLA-B*5801 for prediction of SJS/TEN. The maximum value of the area is 1. The quality of the included studies was generally high (meeting 8 or more of the criteria of the Quality Assessment of Studies of Diagnostic Accuracy-2 (QUADAS-2). 2 studies in the meta-analyses have also been included in this risk analysis separately (Cheng 2015 and Lonjou 2008). 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, but the method of data exaction was not described. Publication bias analysis was not performed. Note: For the population controls, the frequency of patients without HLA-B*5801 is the specificity. Because this does not provide information on the association between HLA-B*5801 and SJS/TEN, the specificity and the with this specificity calculated positive and negative likelihood ratios and area under the summary receiver operating characteristic curve are not included in this risk analysis for the	Author's conclusion: 'The present study reveals that allopurinol is the leading cause of TEN/SJS in many countries. In contrast to carbamazepine, which is ethnic/population specific, the HLA-B*5801 for detecting allopurinol-induced TEN/SJS is universal. Screening of HLA-B*5801 may help patients to prevent the occurrence of allopurinol-induced TEN/SJS, especially in populations with a higher (≥ 5%) risk allele frequency.'

<table>
<tr>
<td>ref. 2, continuation</td>
<td>B*5801: E</td>
<td>meta-analyses with population controls.

Results:
<table>
<tr><td colspan="4">Association between HLA-B*5801 and SJS/TEN</td></tr>
<tr><td colspan="4">in comparison with population controls:</td></tr>
<tr><td></td><td>studies</td><td></td><td>95% CI</td></tr>
<tr><td rowspan="4">diagnostic OR (the odds of having B*5801 for a case relative to the odds of having B*5801 for a control)</td><td>all</td><td>83.5 (S)</td><td>50.7-137.4</td></tr>
<tr><td>European</td><td>58.4 (S)</td><td>16.9-201.5</td></tr>
<tr><td>Han-Chinese</td><td>196.1 (S)</td><td>57.3-672.0</td></tr>
<tr><td>Japanese</td><td>78.8 (S)</td><td>30.4-203.9</td></tr>
<tr><td>sensitivity (part of the cases with B*5801)</td><td>all</td><td>0.78</td><td>0.71-0.85</td></tr>
<tr><td colspan="3">No meta-analysis was performed for the subgroups. In the European studies, sensitivity ranged from 043-0.67, in the Han-Chinese studies from 0.96-1.00, in the Japanese studies from 0.40-0.56. In the Korean study it was 0.80.</td></tr>
<tr><td colspan="4">Heterogeneity between the studies was not-significant for the OR.
Heterogeneity was high for sensitivity.</td></tr>
<tr><td colspan="4">in comparison with allopurinol-tolerant controls (only non-Japanese Asian studies):</td></tr>
<tr><td colspan="2"></td><td></td><td>95% CI</td></tr>
<tr><td colspan="2">diagnostic OR (the odds of having B*5801 for a case relative to the odds of having B*5801 for a control)</td><td>150.7 (S)</td><td>56.9-399.1</td></tr>
<tr><td colspan="2">sensitivity (part of the cases with B*5801)</td><td>0.98</td><td>0.93-1.00</td></tr>
<tr><td colspan="2">specificity (part of the controls without B*5801)</td><td>0.87</td><td>0.84-0.90</td></tr>
<tr><td colspan="2">positive likelihood ratio (ratio of the probability of having SJS/TEN and the probability of not having SJS/TEN for patients with B*5801)</td><td>7.2 (S)</td><td>5.6-9.2</td></tr>
<tr><td colspan="2">negative likelihood ratio (ratio of the probability of having SJS/TEN and the probability of not having SJS/TEN for patients without B*5801)</td><td>0.06 (S)</td><td>0.02-0.13</td></tr>
<tr><td colspan="2">area under the summary receiver operating characteristic curve</td><td>0.95</td><td>0.92-0.98</td></tr>
<tr><td colspan="4">Heterogeneity between the studies was not mentioned.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 3
Saksit N et al.
Risk factors of allopurinol-induced severe cutaneous adverse reactions in a Thai population.
Pharmacogenet Genomics 2017;27:255-63.
PMID: 28509689.</td>
<td>3</td>
<td>In a case-control study, 86 cases with allopurinol-induced severe cutaneous adverse events (51 SJS, 5 SJS/TEN overlap, 11 TEN, and 19 DRESS) were compared with 182 allopurinol-tolerant controls. The tolerant controls were patients from the same hospitals as the cases, who used allopurinol for more than 6 months without any evidence of cutaneous reactions. 27 of the SJS/TEN cases and 54 of the controls were also included in an earlier case-control study, that was not included in this risk analysis separately, but was included in all meta-analyses in this risk analysis. Compared with controls, cases were more often female (52% versus 21%), had a more impaired renal function</td>
<td>Author’s conclusion:
‘Among the risk factors identified, the HLA-B*58:01 allele had the greatest impact on the development of both phenotypes of allopurinol-induced severe cutaneous adverse</td>
</tr>
</table>

<table>
<tr>
<td>ref. 3, continuation</td>
<td>B*5801: F</td>
<td>(estimated glomerular filtration rate 47 versus 59 ml/minute/1.73 m^2), and received more often an allopurinol starting dose higher than recommended on the basis of their estimated glomerular filtration rate (95% versus 77%). However, in multivariate analysis only the effect of female sex remained significant.
11.5% of the controls had HLA-B*5801.
Relevant comedication was not excluded.
ORs were determined by multivariate analysis.

Results of the study:
<table>
<tr><td colspan="3">Association between HLA-B*5801 and severe cutaneous adverse events:</td></tr>
<tr><td>cutaneous adverse event</td><td>$OR_{adjusted}$</td><td>95% CI</td></tr>
<tr><td rowspan="2">all</td><td>229 (S)</td><td>58-899</td></tr>
<tr><td colspan="2">96.5% of the cases had B*5801</td></tr>
<tr><td rowspan="2">SJS/TEN</td><td>175 (S)</td><td>44-691</td></tr>
<tr><td colspan="2">95.5% of the cases had B*5801</td></tr>
<tr><td rowspan="2">DRESS</td><td>149 (S)</td><td>24-∞</td></tr>
<tr><td colspan="2">all cases had B*5801</td></tr>
<tr><td colspan="3">11.4% of cases died in hospital as a result of the severe cutaneous adverse event (8.3% for SJS/TEN and 21.1% for DRESS). 78% of the patients who died were women.</td></tr>
<tr><td colspan="3">Onset of SJS/TEN was after 2-50 days and of DRESS after 10-60 days.</td></tr>
</table>
</td>
<td>reactions in this studied Thai population. In case HLA-B*58:01 genotyping cannot be accessed, close monitoring of allopurinol usage, especially in elderly women with impaired renal function, is necessary to reduce the mortality rate of these life-threatening severe cutaneous adverse reactions.’</td>
</tr>
<tr>
<td>ref. 4
Wu R et al.
Impact of HLA-B*58:01 allele and allopurinol-induced cutaneous adverse drug reactions: evidence from 21 pharmacogenetic studies.
Oncotarget 2016;7:81870-9.
PubMed PMID: 27835909.</td>
<td>4</td>
<td>Meta-analyses of 21 case-control studies with in total 551 patients with allopurinol-induced cutaneous adverse drug reactions. 8 case-control studies had matched allopurinol-tolerant patients as controls, 4 studies had population controls and 9 had both. Of the 9 studies with both kind of controls, 1 (Hung 2005) was only used in the meta-analysis with population controls because of overlap between samples. Part of the cases and tolerant controls in Ng 2016 are also included in Hung 2005. Thus, in the meta-analyses, there were 16 studies with allopurinol-tolerant controls (with in total 551 cases and 2370 controls) and 13 studies with population controls (with in total 414 cases and 9592 controls). 18 of the 21 case-control studies were performed in Asians, 3 in Europeans. All 3 studies in Europeans had population controls (with in total 65 cases and 5137 controls) and 1 had also allopurinol-tolerant controls (25 cases and 23 controls).
All studies analysed severe cutaneous adverse events. 14 studies with allopurinol-tolerant controls and 12 with population controls analysed SJS/TEN. 6 studies with allopurinol-tolerant controls analysed maculopapular exanthema (MPE, in total 99 cases) and 3 studies with allopurinol-tolerant controls erythema exudativum multiforme (EEM, in total 9 cases).
5 studies (4 Asian and 1 European) also had data on the effect of the homozygous HLA-B*5801 genotype.
11 of the 21 studies in this meta-analysis, were included in the meta-analysis of Yu 2017.
3 studies in the meta-analyses have also been included in this risk analysis separately (Ng 2016, Cheng 2015 and Lonjou 2008).
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 data exaction was standardised.
Quality of the included studies was analysed with the Newcastle-Ottawa Scale. Scores ranged from 3 to 8.
Publication bias was assessed, but only for all cutaneous adverse events in all patients.</td>
<td>Author’s conclusion:
‘Our results indicated that allopurinol-severe cutaneous adverse reactions are strongly associated with HLA-B*58:01, and HLA-B*58:01 is a highly specific and effective genetic marker for the detection of allopurinol-induced cutaneous adverse drug reactions, especially for Asian descents.’</td>
</tr>
</table>

ref. 4, continuation

3
B*5801:
E

All significant results were also significant after Bonferroni correction for 9 comparisons ($p < 0,0056$).

Results:

Association between HLA-B*5801 and cutaneous adverse events,

in comparison with population controls:

cutaneous adverse event	ethnicity	OR	95% CI
all	all	100.87 (S)	63.91-159.21
	Caucasian	64.59 (S)	25.42-164.11
	Asian	122.57 (S)	73.79-203.84
	43-64% of the cases in the European studies, 40-55% of the cases in the Japanese studies and 70-100% of the cases in the other Asian studies had B*5801.		
severe	all	108.39 (S)	73.73-159.36
	Caucasian	64.59 (S)	25.42-164.11
	Asian	147.88 (S)	86.69-252.25
SJS/TEN	all	106.48 (S)	65.66-172.66
	Caucasian	58.35 (S)	16.90-201.54
	Asian	156.32 (S)	78.22-312.41

Heterogeneity between the studies was significant and high for all three comparisons in Caucasians.
Heterogeneity between the studies was not significant and moderate for all cutaneous adverse events in all ethnicities.
Heterogeneity was absent or negligible for the other comparisons.
Meta-regression analysis indicated the study size as source of heterogeneity. However, Begg's funnel plot showed no small study effects.

Similar results were obtained after removing each individual study in turn from the meta-analysis.
There were no indications for publication bias.

in comparison with allopurinol-tolerant controls:

cutaneous adverse event	ethnicity	OR	95% CI
all	all	82.77 (S)	41.63-164.58
	Caucasian	39.11 (S)	4.49-340.50
	Asian	87.66 (S)	42.44-181.10
	64% of the cases in the European study, 57% of the cases in the Japanese study and 56-100% of the cases in the other Asian studies had B*5801.		
severe	all	92.06 (S)	59.54-142.32
	Caucasian	39.11 (S)	4.49-340.50
	Asian	95.45 (S)	61.18-148.91
SJS/TEN	all	79.01 (S)	44.23-141.12
	Caucasian	44.00 (S)	3.18-608.16
	Asian	81.42 (S)	44.92-147.51
MPE	all	29.33 (S)	5.89-145.98
	Caucasian	NS	
	Asian	40.45 (S)	6.43-254.57
EEM	all = Asian	12.95 (S)	2.30- 72.85

Heterogeneity between the studies was significant and high for all cutaneous adverse events and MPE in all ethnicities and in Asians.
The OR for the four comparisons in Caucasians was based on only one study.
Heterogeneity was absent for the other comparisons.

<table>
<tr>
<td>ref. 4, continuation</td>
<td></td>
<td>
Meta-regression analysis indicated the study size as source of heterogeneity. However, Begg's funnel plot showed no small study effects.
Similar results were obtained after removing each individual study in turn from the meta-analysis.
There were some indications for publication bias (Egger test: p = 0,05).

Risk of all cutaneous adverse events in comparison with patients heterozygous for or without HLA-B*5801:
<table>
<tr><td></td><td>OR</td><td>95% CI</td></tr>
<tr><td>homozygous HLA-B*5801</td><td>16.78 (S)</td><td>5.90-47.73</td></tr>
<tr><td colspan="3">There was no heterogeneity between the studies.</td></tr>
</table>

For diagnosis of allopurinol-induced cutaneous adverse events, HLA-B*5801 had a specificity of 0.89 and a sensitivity of 0.93. The positive likelihood ratio was 8.24 and the negative likelihood ratio 0.084. The diagnostic odds ratio was 98.59 with significant and very strong heterogeneity.
Univariate meta-regression showed that ethnic population and study size may affect the ability of HLA-B*5801 to diagnose cutaneous adverse events.
</td>
<td></td>
</tr>
<tr>
<td>ref. 5
Ng CY et al.
Impact of the HLA-B(*)58:01 allele and renal impairment on allopurinol-induced cutaneous adverse reactions.
J Invest Dermatol 2016;136:1373-81.
PubMed PMID: 26996548.</td>
<td>3</td>
<td>
In a case-control study, 146 cases with allopurinol-induced cutaneous adverse events were compared with 285 allopurinol-tolerant controls. Of the cases 106 had severe cutaneous adverse events (57 DRESS, 32 SJS (< 10% of the skin detached), 14 SJS/TEN (≥ 10% of the skin detached), 3 DRESS with overlapping SJS/TEN) and 40 maculopapular exanthema (MPE). 12 patients with severe cutaneous adverse events died. The tolerant controls had received allopurinol for at least 6 months without evidence of adverse reactions.
Compared with controls, cases were older (mean 64 years versus 59 years), more often female (45% versus 6%) and had a more impaired renal function (estimated glomerular filtration rate 31 versus 63 ml/minute/1.73 m^2). OR's were corrected for age and sex.
Relevant comedication was not excluded.
The Holm-Bonferroni method was used to correct for 8 comparisons (significance if p < 0,00625).
A meta-analysis of 11 case-control studies with allopurinol-tolerant or population controls, including the one above, was performed. The total number of cases in the meta-analysis was 374.
For SJS/TEN, 7 studies in Asians, 2 in Europeans and 1 in Australians with 164 cases and 8971 controls were included.
For DRESS, 5 studies in Asians, 1 in Europeans and 1 in Australians with 123 cases and 5763 controls were included.
For MPE, 3 studies in Asians, 1 in Europeans and 1 in Australians with 87 cases and 5101 controls were included.
10 of the 11 studies in this meta-analysis, were included in the meta-analysis of Wu 2016, and 8 studies in the meta-analysis of Yu 2017.
2 studies in the meta-analyses have also been included in this risk analysis separately (this study and Lonjou 2008).
A random-effects model was used for the analyses, but prospective registration of the protocol was not mentioned.
There was no clear description of the search and selection strategy and the method of data exaction.
Quality of the included studies and publication bias were not analysed..

Results of the study:
</td>
<td>
Author's conclusion:
'The gene dosage effect of HLA-B*58:01 also influenced the development of allopurinol-induced cutaneous adverse drug reactions (OR = 15.25 for HLA-B*58:01 heterozygotes and OR = 72.45 for homozygotes). Furthermore, coexistence of HLA-B*58:01 and renal impairment increased the risk and predictive accuracy of allopurinol-induced cutaneous adverse drug reactions (heterozygous HLA-B*58:01 and normal renal function: OR = 15.25, specificity = 82%; homozygous HLA-B*58:01 and severe renal impairment: OR = 1269.45, specificity = 100%). This HLA-B*58:01 correlation study suggests that patients with coexisting HLA-B*58:01 and renal impairment (especially estimated glomerular filtra-
</td>
</tr>
</table>

ref. 5, continuation	B*5801: F	Association between HLA-B*5801 and cutaneous adverse events (comparison with patients without HLA-B*5801):	tion rate < 30 ml/minute/1.73 m^2) should be cautious and avoid using allopurinol.'

cutaneous adverse event		OR or $OR_{corrected}$	95% CI
all	all B*5801	23.32 (S)	13.69-39.7
		84% of the cases had B*5801	
		Results were similar after matching for age or sex (OR respectively 22.02 and 21.92).	
	B*5801 heterozygous	17.42 (S)	9.06-33.01
		70% of the cases was heterozygous for B*5801	
		Results were similar after excluding the 3 cases with DRESS with overlapping SJS/TEN (OR = 16.77).	
	B*5801 homozygous	81.47 (S)	19.51-568.95
		14% of the cases was homozygous for B*5801	
		The percentage of homozygotes did not differ between severe cutaneous events and MPE.	
		Results were similar after excluding the 3 cases with DRESS with overlapping SJS/TEN (OR = 80.14).	
severe		44.0 (S)	21.5-90.3
		91% of the cases had B*5801	
		11% of the cases died	
SJS (< 10% skin detached)		32.1 (S)	10.8-95.6
		91% of the cases had B*5801	
SJS/TEN (≥ 10% skin detached)		59.6 (S)	7.6-466.3
		93% of the cases had B*5801	
DRESS		47.7 (S)	18.2-125.4
		91% of the cases had B*5801	
DRESS overlap SJS/TEN		31.9 (S)	1.62-626.6
		100% of the cases had B*5801	
MPE		8.5 (S)	4.2-17.5
		65% of the cases had B*5801	
fatality of cutaneous adverse event		NS	

$OR_{corrected}$ was also corrected for renal function and was calculated for homozygous and heterozygous HLA-B*5801. OR was calculated for the other outcomes.

Association of HLA-B*5801 and baseline renal function (estimated glomerular filtration rate (eGFR) in ml/minute/1.73 m^2) with cutaneous adverse events (comparison with patients without HLA-B*5801 and normal baseline renal function (eGFR > 60 ml/minute/1.73 m^2):

PPV = positive predictive value

	no HLA-B*5801		
eGFR	> 60	30-60	< 30
OR	1.0	NS	3.82 (S)
95% CI			1.8-8.3
sensitivity			92%
specificity			74%
PPV			4%
	HLA-B*5801 heterozygous		
eGFR	> 60	30-60	< 30
OR	15.25 (S)	62.52 (S)	264.31 (S)
95% CI	8.4-27.7	21.7-190.0	87.8-853.7

<table>
<tr>
<td>ref. 5, continuation</td>
<td></td>
<td>
<table>
<tr><td>sensitivity</td><td>84%</td><td>72%</td><td>45%</td></tr>
<tr><td>specificity</td><td>82%</td><td>89%</td><td>96%</td></tr>
<tr><td>PPV</td><td>5%</td><td>7%</td><td>12%</td></tr>
<tr><td></td><td colspan="3">HLA-B*5801 homozygous</td></tr>
<tr><td>eGFR</td><td>> 60</td><td>30-60</td><td>< 30</td></tr>
<tr><td>OR</td><td>72.45 (S)</td><td>300.3 (S)</td><td>1269.45 (S)</td></tr>
<tr><td>95% CI</td><td>14.7-356.7</td><td>47.8-3396.1</td><td>192-15260</td></tr>
<tr><td>sensitivity</td><td>47%</td><td>12%</td><td>6%</td></tr>
<tr><td>specificity</td><td>96%</td><td>99%</td><td>100%</td></tr>
<tr><td>PPV</td><td>13%</td><td>13%</td><td>100%</td></tr>
<tr><td colspan="4">Severe renal impairment at baseline (estimated glomerular filtration rate < 30 ml/minute/1.73 m^2) was an independent risk factor for allopurinol-induced cutaneous adverse events (OR = 4.30; 95% CI 1.96-9.621).</td></tr>
<tr><td colspan="4">HLA-B*5801 is a better predictor of allopurinol-induced cutaneous adverse events than renal function, but the combination is the best predictor.</td></tr>
</table>

Results of the meta-analysis:
<table>
<tr><td colspan="3">Association between HLA-B*5801 and cutaneous adverse events:</td></tr>
<tr><td>cutaneous adverse event</td><td>OR</td><td>95% CI</td></tr>
<tr><td>SJS/TEN</td><td>57.33 (S)</td><td>35.09-93.67</td></tr>
<tr><td></td><td colspan="2">56-67% of the cases in the European studies, 83% of the cases in the Australian study, 20% of the cases in the Japanese study and 80-100% of the cases in the other Asian studies had B*5801.</td></tr>
<tr><td>DRESS</td><td>54.16 (S)</td><td>21.44-138.86</td></tr>
<tr><td></td><td colspan="2">63% of the cases in the European study, 20% of the cases in the Australian study and 92-100% of the cases in the Asian studies had B*5801.</td></tr>
<tr><td>MPE</td><td>NS, trend, p = 0,05</td><td>0.96-32.74</td></tr>
<tr><td></td><td colspan="2">17% of the cases in the European study, 0% of the cases in the Australian study and 0-100% of the cases in the Asian studies had B*5801.</td></tr>
<tr><td colspan="3">Heterogeneity between the studies was significant and high for MPE.
Heterogeneity between the studies was moderate and showed a trend towards significance for DRESS.
Heterogeneity was absent for SJS/TEN.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 6
Jung JW et al.
An effective strategy to prevent allopurinol-induced hypersensitivity by HLA typing.
Genet Med 2015;17:807-14.
PubMed PMID: 25634024.</td>
<td>3</td>
<td>401 patients with chronic renal insufficiency received genotype guided allopurinol therapy for 90 days. 355 patients without HLA-B*5801 received usual allopurinol treatment (starting dose 50 or 100 mg/day), 30 patients with HLA-B*5801 were treated with an allopurinol tolerance induction protocol and 16 patients with HLA-B*5801 received an alternative (benzbromarone (n = 11) or febuxostat (n = 5)). In the allopurinol tolerance induction protocol, the dose was gradually increased from 50 µg/day on day 1-3 to 100 mg/day on day 28 (dose increase every 3 days, dosing scheme 50 µg, 100 µg, 200 µg, 500 µg, 1 mg, 5 mg, 10 mg, 25 mg, 50 mg and 100 mg/day). After the starting dose or tolerance induction, allopurinol doses were adjusted based on renal clearance of the patient. Allopurinol was stopped immediately when hypersensitivity reactions occurred and patients were instructed to report suspicious symptoms immediately. The historical (not genotype guided) incidence of allopurinol-induced severe cutaneous adverse events was estimated from a previous retrospective cohort study (n = 448: 398 without HLA-B*5801 and 50</td>
<td>Author’s conclusion:
‘This study shows the usefulness of HLA-B*58:01 screening in identifying patients at high risk for the development of allopurinol-induced severe cutaneous adverse reactions and suggests that application of a tolerance induction protocol or alternative medications could be an effective strategy to prevent allopuri-</td>
</tr>
</table>

<table>
<tr>
<td>ref. 6, continuation</td>
<td>genotype guided therapy: AA#</td>
<td>with HLA-B*5801).
The frequency of HLA-B*5801 carriers in this Korean population was 12.2%.
Relevant comedication was not excluded.

Results:
<table>
<tr><td colspan="4">Incidence of cutaneous adverse events in comparison with the not genotype guided historical control:</td></tr>
<tr><td colspan="2"></td><td>genotype guided treatment</td><td>incidence in controls</td></tr>
<tr><td rowspan="3">severe cutaneous adverse events</td><td>all patients</td><td>x 0.0 (S)</td><td>2.0%</td></tr>
<tr><td>HLA-B*5801 carriers</td><td>x 0.0 (S)</td><td>18%</td></tr>
<tr><td>patients without HLA-B*5801</td><td>NS</td><td>0.0%</td></tr>
<tr><td rowspan="3">maculo-papular rash</td><td>all patients</td><td>x 2.8 (S)</td><td>1.6%</td></tr>
<tr><td>HLA-B*5801 carriers</td><td>NS</td><td>0.0%</td></tr>
<tr><td>patients without HLA-B*5801</td><td>x 2.7 (S)</td><td>1.8%</td></tr>
<tr><td colspan="4">The authors indicate that the incidence of maculopapular rash may be underestimated in the retrospective control study.</td></tr>
</table>

The authors indicate that the genotype guided therapy reduced the number of patients with severe cutaneous adverse events with approximately 8.28 patient. The costs of treating these patients would have been approximately US$ 400,000. This is 20 times higher than the costs for genotyping HLA-B*5801 in all 401 patients (US$ 19,667).</td>
<td>nol-induced severe cutaneous adverse reactions in HLA-B*58:01-positive patients.’</td>
</tr>
<tr>
<td>ref. 7
Ko TM et al.
Use of HLA-B*58:01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: national prospective cohort study.
BMJ 2015;351:h4848.
PubMed PMID: 26399967.</td>
<td>3

genotype guided therapy: AA#</td>
<td>2742 patients of 14-99 years old (mean 54.9 years) received genotype guided therapy for allopurinol-indications for 2 months. Allopurinol-induced severe cutaneous adverse events always develop within 2 months after starting allopurinol treatment. Chronic tophaceous gout was the indication or one of the indications in 60% of patients, hyperuricaemia in 42% of subjects. 2173 patients without HLA-B*5801 were treated with allopurinol and 569 patients with HLA-B*5801 were treated with an alternative (n = 354; mainly benzbromarone (n = 273), other alternative drugs were febuxostat, colchicine, sulfinpyrazone, brompheniramine, bromhexine, bisoprolol, hydroxychloroquine, sulfasalazine, and sulfonylurea) or continued their prestudy treatment (n = 215; e.g. colchicine and NSAIDs). All subjects were counselled about the risk of severe cutaneous adverse events and asked to return to the hospital immediately in the event that early symptoms developed. The historical (not genotype guided) incidence of allopurinol-induced severe cutaneous adverse events was estimated from a health care database.
The frequency of HLA-B*5801 carriers in this Han-Chinese population from Taiwan was 20%.
Relevant comedication was not excluded.

Results:
<table>
<tr><td colspan="3">Incidence of severe cutaneous adverse events:</td></tr>
<tr><td>genotype guided</td><td>0%</td><td rowspan="2">S</td></tr>
<tr><td>not genotype guided</td><td>0.30%</td></tr>
<tr><td colspan="3">In the genotype guided therapy, severe cutaneous adverse events were also absent after 9 months of follow-up.</td></tr>
<tr><td colspan="3">In the genotype guided therapy, mild cutaneous events developed in 3.6% of patients and there were no hospitalisations due to adverse drug reactions.</td></tr>
</table></td>
<td>Author’s conclusion:
‘Prospective screening of the HLA-B*58:01 allele, coupled with an alternative drug treatment for carriers, significantly decreased the incidence of allopurinol induced severe cutaneous adverse reactions in Taiwanese medical centres.’</td>
</tr>
</table>

<table>
<tr><td>ref. 7, continuation</td><td></td><td>Based on a sensitivity of 100%, a specificity of 85.2% and an incidence of allopurinol-induced severe cutaneous adverse events of 0.30%, the authors calculated a positive predictive value of HLA-B*5801 for development of severe cutaneous adverse events of 2.0%.</td><td></td></tr>
<tr><td>ref. 8
Cheng L et al. HLA-B*58:01 is strongly associated with allopurinol-induced severe cutaneous adverse reactions in Han Chinese patients: a multicentre retrospective case-control clinical study. Br J Dermatol 2015;173:555-8. PubMed PMID: 26104483.</td><td>4

B*5801: E

B*4601: AA#

B*4001, B*3501, B*1502, B*1301, B*5101, B*3901, B*3701, B*2704, B*5502, B*1518, B*3802, B*3503, B*4002, B*4403, B*5102, B*5201, B*5501, B*5601, B*6701: AA</td><td>In a case-control study, 92 cases with allopurinol-induced severe cutaneous adverse events were compared with 75 allopurinol-tolerant controls and 99 healthy controls. Of the cases 41 had DRESS, 33 SJS (< 10% of the skin detached), 7 SJS/TEN (10-30% of the skin detached) and 11 TEN (> 30% of the skin detached). Discontinuation of allopurinol due to severe cutaneous adverse events occurred after 1-64 days of treatment (mean 22 days). The tolerant controls had received allopurinol for at least 3 months without evidence of cutaneous adverse events.
Compared with allopurinol-tolerant controls, cases had more often renal function insufficiency (serum creatinine > 133 µmol/L (male) or > 106 µmol/L (female) for > 6 months) (54% versus 12%).
Relevant comedication was not excluded, but a multivariate analysis taking age, sex, insufficient renal function and comedications into account was also performed for HLA-B*5801.
The Bonferroni method was used to correct for 48 comparisons (48 different HLA-B-alleles; significance if p < 0,001). OR calculation was only for HLA-B-alleles identified in the cases.

Results:
<table>
<tr><td colspan="5">Association between HLA-alleles and severe cutaneous adverse events:</td></tr>
<tr><td rowspan="2">HLA-allele</td><td colspan="2">tolerant controls</td><td colspan="2">healthy controls</td></tr>
<tr><td>OR</td><td>95% CI</td><td>OR</td><td>95% CI</td></tr>
<tr><td>5801</td><td>127.6 (S)</td><td>41-399</td><td>154.9 (S)</td><td>51-472</td></tr>
<tr><td></td><td colspan="4">Results remained significant after correction for age, sex, insufficient renal function and comedications.</td></tr>
<tr><td></td><td colspan="4">95% of the cases had HLA-B*5801</td></tr>
<tr><td>4601</td><td>NS</td><td></td><td>0.30 (S)</td><td>0.15-0.59</td></tr>
<tr><td>4001</td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>3501</td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>1502</td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>1301</td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>5101</td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>3901</td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>3701</td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>2704</td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>5502</td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>1518</td><td>NS</td><td></td><td>-</td><td></td></tr>
<tr><td>3802</td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>3503</td><td>NS</td><td></td><td>-</td><td></td></tr>
<tr><td>4002</td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>4403</td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>5102</td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>5201</td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>5501</td><td>NS</td><td></td><td>-</td><td></td></tr>
<tr><td>5601</td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>6701</td><td>NS</td><td></td><td>NS</td><td></td></tr>
</table>
Based on a sensitivity of 94.6%, a specificity of 88.0% and an incidence of allopurinol-induced severe cutaneous adverse events of 0.2% in Han-Chinese, the authors calculated a positive predictive value of HLA-B*5801 for development of severe cutaneous adverse events of 1.6%.</td><td>Author’s conclusion:
‘Our study shows a strong correlation between HLA-B*58:01 and allopurinol-induced severe cutaneous adverse reactions (SCARs) in the Han Chinese population, by including a considerable pool of patients from various areas of China. In addition, we confirmed that HLA-B*58:01 can be used as a valid genetic marker for allopurinol-induced SCARs in Han Chinese patients. In contrast to the reported 100% linkage between allopurinol-induced SCARs and HLA-B*58:01 in a Han Chinese population, we found that not all allopurinol-induced SCARs can be attributed to HLA-B*58:01.’</td></tr>
</table>

<table>
<tr>
<td>ref. 9
Jung JW et al.
HLA-DR9 and DR14 are associated with the allopurinol-induced hypersensitivity in hematologic malignancy.
Tohoku J Exp Med 2014;233:95-102.
PubMed PMID: 24858023.</td>
<td>3

B58: AA

DR9: B

DR14: B

B48: B

Cw8: AA</td>
<td>453 patients received allopurinol prior to chemotherapy for prevention of tumour lysis-related hyperuricaemia. Median treatment duration was 16.4 days. In accordance with the chemotherapy cycle, allopurinol was taken repeatedly instead of continuously. Follow-up was during and 1 month after treatment.
2.8% of patients experienced maculopapular exanthema (MPE), none experienced severe cutaneous adverse events. The mean interval from allopurinol initiation to symptom onset was 5.5 days. MPE did not recur in 6 patients in which allopurinol was readministered.
In a previous study in Koreans 100% of HLA-B58 was HLA-B*5801.
Relevant comedication was not excluded.

Results:
<table>
<tr><td colspan="5">Association between HLA-alleles and MPE:</td></tr>
<tr><td rowspan="2">HLA-allele</td><td colspan="2">patients who did not develop MPE as controls</td><td colspan="2">population controls</td></tr>
<tr><td>OR</td><td>95% CI</td><td>OR</td><td>95% CI</td></tr>
<tr><td>B58</td><td>NS</td><td></td><td></td><td></td></tr>
<tr><td rowspan="3">DR9</td><td>3.99 (S)</td><td>1.26-12.64</td><td>NS, trend</td><td>0.93-9.08</td></tr>
<tr><td colspan="4">The incidence of MPE in DR9 carriers was 3.7 times that in non-carriers (S).</td></tr>
<tr><td colspan="4">39% of the cases had DR9</td></tr>
<tr><td rowspan="3">DR14</td><td>3.38 (S)</td><td>1.07-10.68</td><td>NS, trend</td><td>0.98-9.63</td></tr>
<tr><td colspan="4">The incidence of MPE in DR14 carriers was 3.2 times that in non-carriers (S).</td></tr>
<tr><td colspan="4">39% of the cases had DR14</td></tr>
<tr><td rowspan="3">B48</td><td>NS, trend</td><td>0.94-13.64</td><td>4.11 (S)</td><td>1.08-15.66</td></tr>
<tr><td colspan="4">The incidence of MPE in B48 carriers and non-carriers was not significantly different (NS).</td></tr>
<tr><td colspan="4">23% of the cases had B48</td></tr>
<tr><td rowspan="3">Cw8</td><td>NS, trend</td><td>0.92-9.10</td><td>NS</td><td></td></tr>
<tr><td colspan="4">The incidence of MPE in Cw8 carriers and non-carriers was not significantly different (NS).</td></tr>
<tr><td colspan="4">39% of the cases had Cw8</td></tr>
</table></td>
<td>Author’s conclusion:
‘Incidence of allopurinol-induced MPE was 2.9% and no case of severe cutaneous adverse reactions was observed when allopurinol was administered to prevent tumor lysis syndrome before chemotherapy. In this setting, allopurinol hypersensitivity reactions were not associated with HLA-B*58:01, but rather had significant association with HLA-DR9 and DR14.’</td>
</tr>
<tr>
<td>ref. 10
Zineh I et al.
Allopurinol pharmacogenetics: assessment of potential clinical usefulness.
Pharmacogenomics 2011;12:1741-9.
PubMed PMID: 22118056.</td>
<td>3</td>
<td>A meta-analysis of 5 case-control studies with 120 cases with severe cutaneous adverse events and 246 allopurinol-tolerant or 2893 population controls was performed.
4 studies were performed in Asians and 1 in Europeans. 1 of the included studies had only allopurinol-tolerant controls, 2 only population controls and 2 both. So, the meta-analysis with tolerant controls included 3 studies with in total 83 cases and the meta-analysis with population controls 4 studies with 93 cases.
All studies in this meta-analysis, were included in the meta-analyses of Yu 2017, Wu 2016 and Ng 2016.
1 study in the meta-analysis has also been included in this risk analysis separately (Lonjou 2008).
A random-effects model was used for the analyses, but prospective registration of the protocol was not mentioned.
There was no clear description of the search and selection strategy and the method of data exaction.
Quality of the included studies was not judged.
Possible publication bias was analysed.

<table>
<tr><td colspan="4">Association of HLA-B*5801 and severe cutaneous adverse events:</td></tr>
<tr><td colspan="2">tolerant controls</td><td colspan="2">population controls</td></tr>
<tr><td>OR</td><td>95% CI</td><td>OR</td><td>95% CI</td></tr>
</table></td>
<td>Author’s conclusion:
‘We performed pooled analyses of the published literature to elucidate the expected risk of severe cutaneous adverse reactions associated with HLA gene variation and associations with HLA-B*5801 to be strong, reproducible and consistent with other observations from genome-wide association studies of other adverse events implicating HLA genes.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 10, continuation</td>
<td>B*5801: E</td>
<td>
<table>
<tr><td>165 (S)</td><td>23-1174</td><td>73 (S)</td><td>32-164</td></tr>
<tr><td colspan="4">56% of the cases in the European study, 40% of the cases in the Japanese study and 80-100% of the cases in the other Asian studies had B*5801.
The pooled sensitivity was 84% and the pooled specificity 95%.</td></tr>
<tr><td colspan="4">There was no significant heterogeneity between the studies.
There were no indications of publication bias.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 11
Somkrua R et al.
Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis.
BMC Med Genet 2011;12:118.
PubMed PMID: 21906289.</td>
<td>4

B*5801: E</td>
<td>
A meta-analysis of 6 case-control studies with 96 SJS/TEN cases and 678 matched allopurinol-tolerant or 3378 population controls was performed. Allopurinol-tolerant controls had used allopurinol for at least 6 months without evidence of any cutaneous reaction. Studies scored 3-7 points of the maximum of 9 points on the Newcastle-Ottowa scale for study quality. 5 studies were performed in Asians and 1 in Europeans. 1 of the included studies had only allopurinol-tolerant controls, 2 only population controls and 3 both. So, the meta-analysis with tolerant controls included 4 studies with in total 55 cases and the meta-analysis with population controls 5 studies with 69 cases.
All studies in this meta-analysis, were included in the meta-analyses of Wu 2016 and Ng 2016, and 5 were included in the meta-analyses of Yu 2017 and Zineh 2011.
1 study in the meta-analysis has also been included in this risk analysis separately (Lonjou 2008).
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 data exaction was standardised.
Quality of the included studies and possible publication bias were analysed.

<table>
<tr><td colspan="4">Association of HLA-B*5801 and SJS/TEN:</td></tr>
<tr><td colspan="2">tolerant controls</td><td colspan="2">population controls</td></tr>
<tr><td>OR</td><td>95% CI</td><td>OR</td><td>95% CI</td></tr>
<tr><td>96.60 (S)</td><td>24.49-381.00</td><td>79.28 (S)</td><td>41.53-151.35</td></tr>
<tr><td colspan="4">For Asian studies the OR was 74.18 (95% CI: 26.95-204.14) and for the single European study 101.45 (95% CI: 44.98-228.82).</td></tr>
<tr><td colspan="4">61% of the cases in the European study, 40% of the cases in the Japanese study and 80-100% of the cases in the other Asian studies had B*5801.</td></tr>
<tr><td colspan="4">There was no heterogeneity between the studies.
There were no indications of publication bias.</td></tr>
</table>
</td>
<td>Author’s conclusion:
‘We found a strong and significant association between HLA-B*5801 and allopurinol-induced SJS/TEN. Therefore, HLA-B*5801 allele screening may be considered in patients who will be treated with allopurinol.’</td>
</tr>
<tr>
<td>ref. 12
Lonjou C et al.
A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs.
Pharmacogenet Genomics 2008;18:99-107.
PubMed PMID: 18192896.</td>
<td>3

B*5801: E</td>
<td>
In a case-control study, the allele frequency of HLA-B*5801 in 31 cases with allopurinol-induced SJS/TEN was compared with the frequency of a mixed Western European population from a database. Of the cases, 27 were of probable European origin and 4 of probable non-European origin.
Relevant comedication was not excluded.
The Bonferroni method was used to correct for 27 comparisons (27 different HLA-alleles; significance if p < 0,0018).

Results:
<table>
<tr><td colspan="3">Association between HLA-B*5801 and SJS/TEN:</td></tr>
<tr><td>ethnic origin</td><td>OR</td><td>95% CI</td></tr>
<tr><td rowspan="2">all</td><td>61 (S)</td><td>32-118</td></tr>
<tr><td colspan="2">61% of the cases had B*5801</td></tr>
<tr><td rowspan="2">European</td><td>80 (S)</td><td>34-187</td></tr>
<tr><td colspan="2">55% of the cases had B*5801</td></tr>
<tr><td colspan="3">In the 12 patients without HLA-B*5801, there was no other HLA-B allele more prevalent than in the general population.</td></tr>
</table>
</td>
<td>Author’s conclusion:
‘At variance with prior results in Asia, this study shows that even when HLA-B alleles behave as strong risk factors, as for allopurinol, they are neither sufficient nor necessary to explain the disease.’</td>
</tr>
</table>

ref. 13 SmPC Zyloric (allopurinol) 12-12-18.	0 HLA-B*5801: E	Warning: The HLA-B*5801 allele has been demonstrated to be associated with the risk of development of allopurinol related hypersensitivity syndrome and SJS/TEN. Prevalence of the HLA-B*5801 allele differs strongly between ethnic groups: up to 20% in Han-Chinese, 8-15% in Thai, approximately 12% in Koreans and 1-2% in people of Japanese or European descent. In patient subgroups known to have a high HLA-B*5801 prevalence, screening for this allele should be considered before start of allopurinol treatment. Chronic kidney disease can further increase the risk in these patients. If HLA-B*5801 genotyping is not available for persons of Han-Chinese, Thai or Korean descent, the benefits of treatment should be carefully considered before treatment start and judged to be larger than the possible higher risks. The usefulness of genotyping has not been established for other patient populations. If a patient is known to be a carrier of HLA-B*5801 (especially in patients of Han-Chinese, Thai or Korean descent), allopurinol should not be started unless there are no other reasonable therapeutic options and the benefits are expected to be larger than the risks. Extra vigilance concerning symptoms of the hypersensitivity syndrome or SJS/TEN is required and the patient should be told to immediately stop treatment when symptoms occur. SJS/TEN can still occur in HLA-B*5801 negative patients, irrespective of their ethnic descent. Adverse events: Rarely: Stevens-Johnson syndrome/toxic epidermal necrolysis The HLA-B*5801 allele has been demonstrated to be associated with the risk of development of allopurinol related hypersensitivity syndrome and SJS/TEN. The usefulness of genotyping as screening instrument for making decisions about treatment with allopurinol has not been established. Administration of allopurinol should immediately be stopped in each patient developing symptoms of SJS/TEN or another severe hypersensitivity reaction. The highest risk of SJS, TEN or other severe hypersensitivity reactions is present within the first weeks of treatment. The best approach in case of such reactions is an early diagnosis and immediate discontinuation of every suspected drug. If allopurinol treatment has been discontinued due to mild skin reactions (i.e. no signs or symptoms of SJS/TEN or another severe hypersensitivity reaction), it is possible, if desired, to start again with allopurinol in a low dose (for example 50 mg/day) followed by gradual dose increase. If the original symptoms reappear, allopurinol should be permanently discontinued, because more severe hypersensitivity reactions can develop.	

Risk group	impaired renal function, comedication with thiazide diuretics, high starting dose, females

Comments:

- For HLA-B*5801, we only included meta-analyses, studies with more than 75 cases or more than 25 European cases and comparisons of genotype-guided with not-genotype-guided therapy in the risk analysis. Other articles on this allele did not contribute enough to the evidence to be included.
  Studies investigating an association between HLA-A*3303, HLA-C*0302 and a six SNP HLA haplotype and allopurinol-induced cutaneous adverse events are not included in the risk analysis, because these associations most probably result from a linkage disequilibrium of these HLA-alleles/haplotype with HLA-B*5801 (Jarjour S et al. Genetic markers associated with cutaneous adverse drug reactions to allopurinol: a systematic review. Pharmacogenomics 2015;16:755-67. PubMed PMID: 25965122 and Génin E et al. Genome-wide association study of stevens-johnson syndrome and toxic epidermal necrolysis in Europe. Orphanet J Rare Dis 2011;6:52. PubMed PMID: 21801394).

- Several studies implicate impaired renal function, leading to diminished clearance of the allopurinol metabolite oxypurinol, as an additional risk factor for allopurinol induced severe cutaneous adverse events (Wang CW et al. Immunopathogenesis and risk factors for allopurinol severe cutaneous adverse reactions. Curr Opin Allergy Clin Immunol 2016;16:339-45. PubMed PMID: 27362322; Ng 2016 (see risk analysis) and Chung WH et al. Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin. Ann Rheum Dis 2015;74:2157-64. PubMed PMID: 25115449).
  Also, *in vitro* studies implicate a role of oxypurinol in the induction of an immunological response to allopurinol (Chung WH et al. Oxypurinol-specific T cells possess preferential TCR clonotypes and express granulysin in allopurinol-induced severe cutaneous adverse reactions. J Invest Dermatol 2015;135:2237-48. PubMed PMID: 25946710; Yun J et al. Oxypurinol directly and immediately activates the drug-specific T cells via the preferential use of HLA-B*58:01. J Immunol 2014;192:2984-93. PubMed PMID: 24591375 and Yun J et al. Allopurinol hypersensitivity is primarily mediated by dose-dependent oxypurinol-specific T cell response. Clin Exp Allergy 2013;43:1246-55. PubMed PMID: 24152157).
- Cost-effectiveness:
  QALY = quality-adjusted life-year
  - 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 2020 Jun 14 (online ahead of print). 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 testing of HLA-B*5801 is more likely to be cost-effective throughout Africa and Asia compared with Europe and the Americas. Genotype-informed allopurinol therapy can be cost-effective throughout most of Africa and Asia with incremental thresholds for cost-effectiveness between US$929 and US$2,130 at a “willingness-to-pay” threshold of US$40,000, with the exception of Zambia and Japan where HLA-B*5801 is rare. In contrast, pre-emptive testing of HLA-B*58:01 is unlikely to be cost-effective in Belgium, the Czech Republic, Estonia, and Ireland, as well as Serbia and the United Kingdom. In the United States, alternative treatment thresholds differ considerably between subpopulations. Here, pre-emptive HLA-B*5801 testing is more likely to be cost-effective for African (total cost by which the alternative treatment can exceed the cost of allopurinol for the genotype-guided strategy to be cost-effective at a at a “willingness-to-pay” threshold of US$40,000 up to $5,019) and Asian Americans (total cost by which the alternative treatment can exceed the cost of allopurinol for the genotype-guided strategy to be cost-effective at a at a “willingness-to-pay” threshold of US$40,000 up to $5,217) compared with White and Hispanic Americans (total cost by which the alternative treatment can exceed the cost of allopurinol for the genotype-guided strategy to be cost-effective at a at a “willingness-to-pay” threshold of US$40,000 up to $2,835 and $4,219, respectively), in agreement with previous reports. However, HLA-B*5801 screening is unlikely to be both better and cheaper than allopurinol for all in any population analysed.
    Allopurinol for all was compared with genotype-guided therapy, consisting of an alternative drug for HLA-B*5801 positive patients and allopurinol for HLA-B*5801 negative patients.
    In case of countries with heterogeneous population structures, the authors aggregated subpopulation-specific HLA-B*5801 frequency information based on the national population composition. For countries with no available information on allele frequency, they used the averaged continental allele frequency to calculate the number of carriers per continent.
    The authors reported a high HLA-B*5801 frequency in Whites in Australia (frequency for all Australians 4.7%), but not in New Zealand (frequency for the whole population 0.5%).
    Direct medical costs were calculated. The calculation was based on a price of treatment of SJS/TEN of US$ 16,491, a price of treatment of DRESS of US$ 16859, and genotyping costs of US$ 40. Due to a strong variation of drug prizes across the world, drug prizes were not included, but the total cost by which the alternative treatment can exceed the cost of allopurinol for the genotype-guided strategy to be cost-effective were calculated. Positive and negative predictive values for SJS/TEN/DRESS development and HLA-B*5801 (1.3% and 100% respectively) were obtained from literature (Phillips EJ et al. Pharmacogenetics of drug hypersensitivity. Pharmacogenomics 2010;11:973-87. PMID: 20602616; the cost-effectiveness analysis of Plumpton 2017; and Tassaneeyakul W et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. Pharmacogenet Genomics 2009;19:704-9. PMID: 19696695).
    Recommendations remained largely unaffected when genotyping costs of US$141 instead of US$40 were used in the calculations.
  - Pruis SL et al. Cost-effectiveness of sequential urate lowering therapies for the management of gout in Singapore. J Med Econ 2020;23:838-47. PMID: 32301360.
    In 50-year old Singaporean patients with symptomatic gout (serum uric acid ≥ 8 mg/dL), treatment strategies incorporating HLA-B*5801 genotyping before sequential urate lowering therapy use (followed by withholding allopurinol in HLA-B*5801 carriers), resulted in less QALYs and were more expensive than the corresponding non-genotyping strategies. Three treatment strategies were tested. The first was allopurinol 300 mg/day, followed by allopurinol 600 mg/day in the event of insufficient response for 6 months, and probenecid if response remained insufficient for another 6 months (with febuxostat 80 mg/day added as possible alternative for probenecid for HLA-B*5801 carriers in the corresponding genotype-guided strategy). The second was

allopurinol 300 mg/day, followed by allopurinol 600 mg/day, followed by probenecid, followed by febuxostat 80 mg/day. The third was allopurinol 300 mg/day followed by febuxostat 80 mg/day in patients with gout and concomitant moderate to severe renal impairment (chronic kidney disease stage ≥3 b, with estimated glomerular filtration rate <45 mL/min).
The threshold SJS/TEN incidence above which the genotype-guided treatment strategy (probenecid, febuxostat for HLA-B*5801 carriers and allopurinol 300 mg/day, allopurinol 600 mg/day, probenecid for non-carriers) produced incremental QALYs over the non-genotyping strategy (all patients treated as the non-carriers) was 1.12%. Above an incidence of 1.5%, the genotype-guided strategy was both better and cheaper than the non-genotyping strategy.
Costs were evaluated from the perspective of Singapore healthcare payers. Lifelong medical costs were calculated (over a time period of 30 years for patients with a mean age of 50 years at treatment start). The calculation was based on a price of allopurinol initiation, maintenance with 300 mg/day and maintenance with 600 mg/day in the primary or tertiary setting of Singapore dollars (SG$) 291/3 months and SG$ 1,036/3 months, SG$ 58/3 months and SG$ 138/3 months, and SG$ 72/3 months and SG$ 152/3 months respectively, a price of febuxostat initiation and maintenance in the primary and tertiary setting of SG$ 526/3 months and SG$ 1,023/3 months, and SG$ 337/3 months and SG$ 417/3 months respectively, a price of probenecid initiation and maintenance in the primary and tertiary setting of SG$ 287/3 months and SG$ 826/3 months, and SG$ 92/3 months and SG$ 172/3 months respectively, treatment costs of an acute flare (in the primary setting) of SG$ 113, a price of treatment of non-fatal and fatal SJS of SG$ 21,663 and SG$ 63,457 respectively, a price of treatment of non-fatal and fatal SJS/TEN-overlap of SG$ 45,337 and SG$ 86,324 respectively, a price of treatment of non-fatal and fatal TEN of SG$ 59,523 and SG$ 88,470 respectively, a price of treatment of (non-fatal) DRESS of SG$ 6,740, a price of treatment of ocular complications from non-fatal and fatal severe cutaneous adverse events of SG 2,505 and SG$ 717 respectively (either once for once-off complications or every 3 months for recurring complications), and genotyping costs of SG$ 280. The 0.2% incidence rate of allopurinol-induced SJS/TEN and 0.08% incidence rate of allopurinol-induced DRESS were derived from literature (the cost-effectiveness analyses of Saokaew 2014 and Dong 2015), as were the 0.46% incidence of SJS/TEN in patients with renal impairment (the cost-effectiveness analysis of Ke 2017), the 0.01% incidence of febuxostat-induced SJS/TEN and the mortality rates of severe cutaneous adverse events. In the calculations, each 2 mg/dL over the serum uric acid target of 6 mg/dL resulted in a reduced quality of life. The proportions of patients who achieved target serum uric acid (<6 mg/dL) with first-line allopurinol or febuxostat were derived by conducting a network meta-analysis of randomized controlled trials, as were the discontinuation rates due to adverse events during the first 3 months of treatment. Response rates of allopurinol 600 mg/day and response rates and discontinuation rates of probenecid were also derived from literature. The rates of allopurinol- and febuxostat-induced flares were derived from literature, that for probenecid was assumed to be the same as that for allopurinol. In Singapore, the weighted prevalence of HLA-B*5801 is 18.5% with varying rates occurring across different ethnic groups.

- Teng GG et al. Is HLA-B*58:01 genotyping cost effective in guiding allopurinol use in gout patients with chronic kidney disease? Pharmacogenomics 2020;21:279-91. PMID: 32180492.
In Singaporean patients with symptomatic hyperuricemia and chronic kidney disease (estimated glomerular filtration rate < 60 ml/min), HLA-B*5801-guided therapy was less cost-effective than allopurinol for all, followed by febuxostat in non-responders. In addition, HLA-B*5801-guided therapy was not cost-effective at a willingness-to-pay threshold of US$ 50,0000 per QALY gained with costs of US$ 269,147 per QALY gained when calculated over a 1-year period and increasing to US$ 741,544 per QALY gained when calculated over a 15-year period (lifelong). Genotype-guided therapy consisted of febuxostat for HLA-B*5801 carriers and allopurinol followed by febuxostat in non-responders for non-carriers. HLA-B*5801-guided therapy was both better and cheaper than febuxostat for all. When compared to treatment with allopurinol alone without switching to febuxostat for non-responders, the genotyping strategy is cost effective, but this may not mirror clinical practice. The maximum dose used was 300 mg/day for allopurinol and 80 mg/day for febuxostat.
The period over which the costs were calculated and the severe cutaneous adverse event incidence were the most influential factors in the cost-effectiveness calculations.
Costs were evaluated from a health systems perspective, which informs governments' public health policy decisions, to prioritize services and healthcare products that should receive subsidies or reimbursements from a limited pool of funds. Medical costs were calculated over a 1-year period, but also over a 15-year period (corresponding to lifelong for patients with chronic kidney disease). The calculation was based on a price of allopurinol of US$ 23/year, a price of febuxostat of US$ 750/year, a price of treatment of SJS of US$ 4,200, a price of treatment of SJS/TEN-overlap of US$ 12,390, a price of treatment of TEN of US$ 20,590, a price of treatment of long-term complications from SJS/TEN (dry eye syndrome and psychological sequelae) of US$ 580/year, a price of hospital admission for gout of US$ 2,324, a price of a visit to a specialist of US$ 90, and genotyping costs of US$ 150. The 0.46% incidence rate of allopurinol-induced severe cutaneous adverse events was derived from literature (the cost-effectiveness analysis of Ke 2017), as was the mean pooled sensitivity and specificity of the HLA-B*5801 test for SJS/TEN and DRESS of 94 and 86.5% respectively (the cost-effectiveness analysis of Plumpton 2017). Based on these numbers, the positive predictive value of the genotyping test is 3.0% and the negative predictive value is nearly 100%. Response rates for allopurinol and febuxostat were taken from the US package insert. The incidence rates of long-term complications and the mortality rates due to SJS/TEN were derived from literature. The HLA-B*5801 carrier frequency in Singapore is 18.5%.

The results are most sensitive to severe cutaneous adverse event incidence. If a high-risk population can be identified that has an allopurinol-induced severe cutaneous adverse event rate greater than 1.2%, then genotyping would become cost effective for a 1-year time horizon. A two-way sensitivity analysis of severe cutaneous adverse event incidence and genotyping cost illustrates that if the genotyping cost were only US$ 32, as in Thailand, then a severe cutaneous adverse event incidence of 0.61% would achieve additional costs of US$ 50,000 per QALY gained. When the genetic test price is reduced to zero (e.g., the person's HLA-B*5801 status is known from a previous genetic screen), the genotyping strategy will meet the willingness-to-pay threshold at current severe cutaneous adverse event incidence and 1-year time horizon. When the cost of genetic testing is <US$ 20 and the annual cost of febuxostat 80 mg/day to the healthcare system is <US$ 500, genetic testing would fall below the willingness-to-pay threshold of US$ 50,000 per QALY gained.
At a willingness-to-pay threshold of US$ 50,000 per QALY gained, varying all parameters simultaneously showed that the chance of allopurinol for all patients being optimal is 84.4%, with only a chance of 15.5% for HLA-B*5801-guided therapy and 0.1% for febuxostat for all.

- Chong HY et al. Cost-effectiveness analysis of HLA-B*58: 01 genetic testing before initiation of allopurinol therapy to prevent allopurinol-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in a Malaysian population. Pharmacogenet Genomics 2018;28:56-67. PMID: 29176400.
Compared with allopurinol for all, both HLA-B*5801 guided therapy and probenecid for all in resulted in less QALYs and higher costs in 50-year old Malaysian patients with chronic gout and normal kidney function. HLA-B*5801 guided therapy consisted of probenecid 2 g/day for HLA-B*5801 positive patients and allopurinol for HLA-B*5801 negative patients. At the cost-effectiveness threshold of US$ 8695 per QALY, the probability of allopurinol for all being the best choice is 99.9%, in contrast with 0.1 and 0% in HLA-B*58:01 screening and probenecid for all, respectively. This is because of the low incidence of allopurinol-induced SJS/TEN in Malaysia and the lower efficacy of probenecid compared with allopurinol in gout control.
In patients who did not achieve the target serum uric acid level with allopurinol 300 mg/day, the dose was increased to 600 mg/day. Patients who developed allopurinol-induced SJS/TEN and those who did not respond to allopurinol 600 mg/day were switched to probenecid. Patients who did not respond to probenecid 2 g/day continued probenecid treatment for lifetime, and acute gout flares were treated.
HLA-B*5801 guided therapy resulted also in less QALYs and higher costs if febuxostat was used in HLA-B*5801 positive patients instead of probenecid. In addition, febuxostat for all resulted also in less QALYs and higher costs then allopurinol for all. In the calculations, febuxostat was considered less effective than allopurinol 600 mg/day (probability of achieving target serum uric acid levels of 0.69 and 0.78, respectively).
Costs were evaluated from a societal perspective. Lifelong direct medical costs, direct non-medical costs (costs of transportation and additional food), and indirect costs (productivity loss because of illness) were calculated. Costs were given in the Malaysian currency MYR. In 2016, MYR 4.49 was equivalent to US$ 1. The calculation was based on a price of allopurinol of MYR 0.14/300 mg tablet, a price of probenecid of MYR 0.33/500 mg tablet, a price of febuxostat of MYR 8.9/80 mg tablet, costs of an SJS/TEN event of MYR 6462.12, costs of treatment of dry eye syndrome of MYR 561.69/year, costs of gout management of MYR 638.70 for the first year and MYR 319.35/year for the subsequent years, costs of acute gout flare management of MYR 914.28/year, and genotyping costs of MYR 287.17. The incidence of allopurinol-induced SJS/TEN in Malaysia was assumed to be 0.2% (Hung S-I et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci USA 2005;102:4134-9). Based on the association between HLA-B*5801 and allopurinol-induced SJS/TEN, incidences of allopurinol-induced SJS/TEN in patients with and without HLA-B*5801 were calculated to be 1.5 and 0%, respectively, The probability of death caused by allopurinol-induced SJS/TEN (4.17%) was derived from literature, as was the 40.6% probability of developing long-term ocular sequelae of SJS/TEN (dry eye syndrome). The probabilities of achieving target uric acid levels with allopurinol 300 mg/day, allopurinol 600 mg/day, probenecid 2 g/day and febuxostat 80 mg/day were obtained from literature. The ethnicity-weighted prevalence of HLA-B*5801 carriers was estimated to be 12.2% in Malaysia.
The effectiveness of probenecid 2 g/day in achieving target serum uric acid level had the highest potential influence on both additional costs and QALYs gained. The other key drivers on the incremental cost were the length of inpatient stay because of uncontrolled gout and the number of outpatient visits because of acute gout flare, whereas the discounting rate for outcomes (i.e. the assumed decrease in the effect of outcomes on quality of life in time due to medical progress) and the probability of achieving target serum uric acid level with allopurinol 600 mg/day had the greatest potential effect on the QALYs gained.
- Plumpton CO et al. Cost effectiveness analysis of HLA-B*58:01 genotyping prior to initiation of allopurinol for gout. Rheumatology (Oxford) 2017;56:1729-39. PMID: 28957559.
The authors conclude that routine testing for HLA-B*5801 in order to reduce the incidence of adverse drug reactions in patients being prescribed allopurinol for gout is unlikely to be cost-effective in the UK; however testing is expected to become cost-effective with reductions in the cost of genotyping, and with the future availability of cheaper, generic febuxostat.
Compared with allopurinol for all, HLA-B*5801 guided therapy for chronic gout patients of 61.6 years old from the UK (81% male) is not cost-effective (additional costs of £44,954 per QALY gained for all patients and £38,478 per QALY gained for patients with chronic renal insufficiency), using the willingness-to-pay threshold of £30,000/QALY. Genotype guided therapy consisted of allopurinol for patients without HLA-B*5801 and febuxostat for patients with HLA-B*5801. The probability of testing being cost-effective at the willingness-to-pay threshold was 0.25. Reduced costs of testing or febuxostat resulted in cost-effectiveness (costs below £30,000/QALY).

Patients were titrated to allopurinol 300 mg/day during the first 3 months. Patients who are genotyped for HLA-B*5801 or who experience a serious adverse drug reaction with allopurinol switched to febuxostat 80 mg/day. Patients experiencing a serious adverse drug reaction with febuxostat (which is far less likely), discontinued urate lowering therapy altogether. Prophylactic treatment with colchicine (0.5 mg twice daily) was assumed for 3 months following initiation of allopurinol, or for 6 months following initiation of febuxostat. The use of NSAIDs was assumed for all patients. Patients with chronic renal insufficiency were treated with allopurinol 100 mg/day and colchicine 0.5 mg/day.
According to the calculations, HLA-B*5801 guided therapy would be cost-effective within populations with a higher prevalence of HLA-B*5801 (at £27,218 and £22 359 per QALY gained, for 4.24% and 17% prevalence, respectively). HLA-B*5801 guided therapy would also be cost-effective when the costs of febuxostat would be reduced to that of allopurinol, resulting in additional costs of £23,679 per QALY gained, and when the genotyping costs would be reduced from a mean £55.36 per person to £20, resulting in additional costs of £29,469 per QALY gained. In the case of both reduced price febuxostat and cheaper testing, the additional costs per QALY gained would be £8,195.
Costs were evaluated from the perspective of the National Health Service in the UK. Lifelong medical costs were calculated. The calculation was based on a price of allopurinol of £3.77/300mg, a price of febuxostat of £79.17/80mg, a price of colchicine of £65.92/1mg, a price of treatment of SJS/TEN of £31,232.00, a price of treatment of long-term complications from SJS/TEN of £140.00, a price of treatment of DRESS of £11,209.03, a price of treatment of a gout flare of £321.62, costs for gout management of £97.40/3 months, HLA-B*58 screening costs of £54.29, and genotyping costs (HLA-B*5801 screening) in HLA-B*58 positive patients of £94.91. The incidence rates of allopurinol-induced SJS/TEN and DRESS (0.02% and 0.11%, respectively) (the cost-effectiveness analysis of Saokaew 2014 and 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; McInnes GT et al. Acute adverse reactions attributed to allopurinol in hospitalised patients. Ann Rheum Dis 1981;40: 245-9) and febuxostat-induced SJS/TEN and DRESS (both 0.01%) were derived from literature, as were the sensitivities and specificities of the HLA-B*5801 test for SJS/TEN and DRESS, the 26.52% and 10% mortality rates of SJS/TEN and DRESS, respectively, and the 3.79 fold increase in SJS/TEN rate and the 67% mortality rate of SJS/TEN in patients with chronic renal insufficiency. Effectiveness data of allopurinol and febuxostat and risks of initial and acute flares were also derived from literature. In the calculations, febuxostat was assumed to be more effective than allopurinol. The HLA-B*5801 carrier frequency in the UK was assumed to be the European mean of 1.13%.
The effectiveness of febuxostat (risk ratio for achieving serum uric acid <360 µmol/L vs allopurinol) and the cost of genotyping were most influential. The additional costs per QALY gained were stable to variation in all other parameters used in the calculation within their 95% confidence intervals.

- Ke CH et al. Cost-effectiveness analysis for genotyping before allopurinol treatment to prevent severe cutaneous adverse drug reactions. J Rheumatol 201744:835-43. PMID: 28365572.
  Compared with benzbromarone for all, HLA-B*5801 guided allopurinol therapy for 54-year old Taiwanese patients with hyperuricemia (76.5% male, 64.6% gout patients) with or without chronic kidney disease is cost-effective (New Taiwan (NT) $234,610 (US$7508) per QALY gained for all patients and NT$230,925 (US$ 7390) per QALY gained for patients with chronic kidney disease). In contrast, compared to benzbromarone for all, allopurinol for all was both more expensive and less effective. The same was true for febuxostat for all. Genotype-guided treatment consisted of allopurinol for patients without HLA-B*5801 and either benzbromarone or febuxostat for patients with HLA-B*5801. Patients on benzbromarone could be switched to febuxostat within 1 year in case of intolerance or insufficient response.
  The study results were sensitive to the probability of benzbromarone/febuxostat-related hypersensitivity, and the negative predicted value of genotyping.
  Costs were evaluated from the Taiwanese health care payer (the National Institute of Health) perspective. Medical costs were calculated for treatment during 1 year. The calculation was based on costs of allopurinol of NT$ 257/year, costs of febuxostat of NT$ 4856/year, costs of benzbromarone of NT$ 426/year, a price of treatment of non-fatal severe cutaneous adverse events of NT$ 92,091, a price of treatment of fatal severe cutaneous adverse events of NT$ 264,140, gout- or hyperuricemia-related costs of NT$ 38,668/year, costs for patients with chronic kidney disease of NT$ 66,885/year, and genotyping costs of NT$ 2648 (US$ 87.70). The incidence of allopurinol-induced severe cutaneous adverse events (0.222% in the total population and 0.455% in patients with chronic kidney disease) and the 10.2% mortality rate of allopurinol-induced severe cutaneous adverse events were derived from a health information database. The association between allopurinol-induced severe cutaneous adverse events and HLA-B*5801 in the Taiwanese population was derived from literature (Pavlos R et al. HLA and pharmacogenetics of drug hypersensitivity. Pharmacogenomics 2012;13:1285-30, and Zineh 2011). From this, the probability of allopurinol-induced severe cutaneous adverse events in patients with/without HLA-B*5801 was calculated to be 1.21% and 0.0048% for all patients, and 2.48% and 0.0099% in patients with chronic kidney disease. The probability of switching urate-lowering therapy was derived from hospital data, and the incidence of severe cutaneous adverse events induced by benzbromarone or febuxostat was assumed to be very rare, i.e. 1 per 10,000 persons (0.01%). The HLA-B*5801 carrier frequency in Taiwan is 18%.
- Jutkowitz E et al. The cost-effectiveness of HLA-b*5801 screening to guide initial urate-lowering therapy for gout in the United States. Semin Arthritis Rheum 2017;46:594-600. PubMed PMID: 27916277.
  Compared with allopurinol for all, HLA-B*5801 guided therapy for gout patients of 53 year old from the USA is cost-effective for African Americans (costs US$ 83,450/quality-adjusted life year (QALY) gained) and Asians

in the USA (costs US$ 64,190/QALY), but not for Caucasians or Hispanics (costs US$ 183,720/QALY), using the accepted US willingness-to-pay threshold (US$109,000/QALY). Results were robust in sensitivity analyses, except that reducing the risk of SJS/TEN by a half made testing not cost-effective for all races/ethnicities. Genotype guided therapy consisted of allopurinol for patients without HLA-B*5801 and febuxostat for patients with HLA-B*5801. Patients on allopurinol were switched to febuxostat if allopurinol was ineffective or not tolerated. In the US, the allele frequency of HLA-B*5801 is 0.7% in Caucasians and Hispanics, 3.8% in African Americans and 7.4% in Asians.

In a previous analysis, the authors found that febuxostat for all patients was not cost-effective (dominated by current options).

Costs were evaluated from the perspective of a US healthcare payer. Lifelong medical costs were calculated. For Caucasians and Hispanics, the calculated costs were US$ 23,777 and the calculated QALYs 13.2248 for allopurinol for all patients and the calculated costs were US$ 23,966 and the calculated QALYs 13.2258 for the genotype guided therapy. For African Americans, the calculated costs were US$ 23,826 and the calculated QALYs 13.2205 for allopurinol for all patients and the calculated costs were US$ 24,280 and the calculated QALYs 13.2259 for the genotype guided therapy. For Asians, the calculated costs were US$ 23,898 and the calculated QALYs 13.2141 for allopurinol for all patients and the calculated costs were US$ 24,648 and the calculated QALYs 13.2257 for the genotype guided therapy. The calculation was based on a price of allopurinol of US$ 72/year, a price of febuxostat of US$ 2213/year, a price of treatment of SJS/TEN of US$ 45,661, a price of treatment of other hospitalized cutaneous adverse reactions of US$ 6180, a price of treatment of long-term complications from SJS/TEN of US$ 980/year, and genotyping costs of US$ 129. The 0.026% incidence rate of allopurinol-induced SJS/TEN in US Caucasians and the 30% incidence rate of death due to SJS/TEN were derived from literature (Kim SC et al. Severe cutaneous reactions requiring hospitalization in allopurinol initiators: a population-based cohort study. Arthritis Care Res 2013;65:578–84), as were the relative incidences in different US ethnicities (Lu N et al. Racial disparities in the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis as urate-lowering drug adverse events in the US. Semin Arthritis Rheum 2016;46:253–8). Based on these relative incidences, an incidence of 0.026%, 0.136% and 0.298% was calculated for allopurinol-induced SJS/ TEN in Hispanics, Africans-Americans and Asians respectively. With the sensitivity and specificity values of Zineh 2011 (Zineh I et al. Allopurinol pharmacogenetics: assessment of potential clinical usefulness. Pharmacogenomics 2011;12:1741–9), positive predictive values for SJS/TEN development in HLA-B*5801 carriers were calculated to be 0.472% for US Caucasians and Hispanics, 2.421% for African Americans, and 5.164% for US Asians. The 19% incidence rate of long-term complications due to SJS/TEN was derived from literature.

Genotype guided therapy is cost-effective when the prevalence of HLA-B*5801 is greater than 1.6%. For testing to be cost-effective in Caucasians and Hispanics, the genotyping test would have to cost less than US$ 52.

When the costs of febuxostat would increase by 50%, genotype guided therapy for African Americans would no longer be cost effective (costs US$ 118.000/QALY). Change in the price of febuxostat did not substantially alter the costs per QALY gained for Caucasians and Hispanics or Asians.

- Plumpton CO et al. A systematic review of economic evaluations of pharmacogenetic testing for prevention of adverse drug reactions. Pharmacoeconomics 2016;34:771-93. Review. PubMed PMID: 26984520.

  The authors performed a systematic literature review of economic evaluations of pharmacogenetic tests of HLA-B*5801 prior to allopurinol. They conclude that evidence exists to support the cost-effectiveness of genotyping HLA-B*5801 prior to allopurinol, with the two available high-quality studies in two different populations indicating that genotyping was either dominant or cost-effective. However, HLA-B*5801 is particularly prevalent in Asian populations, and whilst testing prior to the use of allopurinol is cost-effective for these populations, the result may not hold for populations with a low frequency of HLA-B*5801.

  Two economic evaluations were retrieved for HLA-B*5801: one conducted in Thailand (Saokaew 2014) and one in Korea (Park 2015). Park 2015 was a cost-effectiveness analysis, Saokaew 2014 a cost-utility analysis. The cost perspective was that of the healthcare provider in Park 2015, whereas Saokaew 2014 used a societal perspective. The quality of reporting in the economic evaluations was high for both studies (96% for Saokaew 2014 and 86% for Park 2015). High quality was defined as reporting of more than 85% of items on a 24-item checklist for economic health evaluations. Park 2015 stated that the evidence supporting the effectiveness was retrieved from ‘literature searches’, Saokaew 2014 from ‘hospital data’.

  Both studies considered the cost effectiveness of genotyping prior to prescription of allopurinol in gout, finding genotyping to be either dominant, i.e. both better and cheaper, (Park 2015) or cost-effective (Saokaew 2014). Park 2015 found genotype guided therapy to cost US$ 138 less. Saokaew 2014 found genotype guided therapy to cost Thai Baht (THB) 156,937/QALY gained ($US1 = THB 41.54). Despite evidence being in favour of testing, there are no current FDA or EMA recommendations, while the American College of Rheumatology guidelines recommend genotyping patients at high risk of adverse drug reactions, including those with chronic renal insufficiency.

- Dong D et al. Cost-effectiveness analysis of genotyping for HLA-B*5801 and an enhanced safety program in gout patients starting allopurinol in Singapore. Pharmacogenomics 2015;16:1781-93. PubMed PMID: 26554739.

  Based on a cost-effectiveness threshold of US$ 50,000 per quality-adjusted life year, genotype-guided urate-lowering therapy selection or enhanced safety program for Singaporean patients with chronic gout without chronic kidney disease, was not cost-effective. Avoidance of urate-lowering therapy was the least preferred strategy as uncontrolled gout leads to lower quality-adjusted life years and higher costs.

This study compared six strategies, of which 3 genotype guided. The first is standard urate-lowering therapy with allopurinol as first-line drug. The second is allopurinol as a first-line drug coupled to an enhanced safety program. The third is a genotype guided therapy in which patients with HLA-B*5801 receive probenecid and patients without HLA-B*5801 allopurinol. The fourth is the same as the third, but with a switch of patients with HLA-B*5801 who do not respond to probenecid to allopurinol combined with the enhanced safety program. The fifth is a genotype guided therapy in which patients with HLA-B*5801 receive allopurinol combined with the enhanced safety program and patients without HLA-B*5801 allopurinol without the enhanced safety program. The sixth is no urate-lowering therapy and treatment of acute flares only.
The enhanced safety program was a 3-month monitoring program consisting of a nurse-led face-to-face patient education session on SJS/TEN at drug initiation, six fortnightly phone calls to check for early signs of SJS/TEN and remind patients to use a hotline for reporting any symptoms of emerging adverse drug reactions for appropriate medical attention. The rationale for this safety program was that it has been shown that early withdrawal of causative drugs among SJS/TEN patients is associated with a lower risk of dying (OR = 0.69) (Garcia-Doval I et al. Toxic epidermal necrolysis and Stevens–Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? Arch Dermatol 2000;136:323-7).
Three strategies were more expensive and less effective than standard allopurinol: no urate-lowering therapy, genotype guided therapy with probenecid for patients with HLA-B*5801 and genotype guided therapy with allopurinol combined with an enhanced safety program for patients with HLA-B*5801. When febuxostat was modelled as an additional option, genotype guided therapy with an alternative for patients with HLA-B*5801 still yielded fewer quality adjusted life years (QALYs) and incurred higher costs.
After removing these strategies, compared with standard allopurinol, the costs per QALY gained were US$ 79,140 for standard allopurinol combined with the enhanced safety program and US$ 164,770 for the genotype guided therapy with probenecid for patients with HLA-B*5801 and a switch to allopurinol and the enhanced safety program for non-responders to probenecid. Both values were above a commonly accepted threshold of US$50,000 per QALY for cost-effectiveness.
The authors conclude that:

- Genetic testing-guided urate-lowering therapy treatment that avoids allopurinol in HLA-B*5801-positive patients is more costly and yields lower quality-adjusted life years due to additional testing costs, higher drug costs (e.g., febuxostat) or usage of a less efficacious drug (e.g., probenecid) and inadvertently denies 18.5% of patients (HLA-B*5801 carriers in the Singapore population) of an effective drug when only 1.5% will develop Stevens–Johnson syndrome/toxic epidermal necrolysis.
- Genetic testing-guided urate-lowering therapy with an enhanced safety program, in which HLA-B*5801-positive patients are initially given probenecid, but non-responders are switched to allopurinol under an enhanced safety program, currently is not cost effective. It becomes cost-effective if the genetic test cost drops below US$90.
- Without genetic testing, implementing a safety program consisting of more frequent monitoring for early signs of adverse drug reactions during the first 3 months for all patients initiating allopurinol as a first-line drug becomes cost effective when the safety program costs less than US$39 per patient.

Costs were evaluated from the perspective of the Singapore health system. Lifelong direct medical costs were calculated for a period of 30 years. For standard allopurinol for all patients, the calculated costs were US$ 4,131 and the calculated QALYs 14.9966. For allopurinol and the enhanced safety program for all patients, the calculated costs were US$ 4,194 and the calculated QALYs 14.9974. For genotype guided therapy with allopurinol and the enhanced safety program for patients with HLA-B*5801, the calculated costs were US$ 4,419 and the calculated QALYs 14.9974. For genotype guided therapy with probenecid for patients with HLA-B*5801 and a switch to allopurinol and the enhanced safety program in case of non-response, the calculated costs were US$ 4,588 and the calculated QALYs 15.0020. For genotype guided therapy with probenecid for patients with HLA-B*5801, the calculated costs were US$ 5,160 and the calculated QALYs 14.9597. For no urate-lowering therapy for all patients, the calculated costs were US$ 15,310 and the calculated QALYs 14.1319. The calculation was based on a price of allopurinol of US$ 33/year (up to 300 mg/day) or US$ 66/year (up to 600 mg/day), a price of probenecid of US$ 132/year (up to 2 g/day), a price of treatment of SJS of US$ 3477, a price of treatment of SJS/TEN of US$ 10,254, a price of treatment of TEN of US$ 17,031, a price of treatment of an acute gout flair of US$ 22, a price of treatment of long-term complications from SJS/TEN of US$ 200/year, and genotyping costs of US$ 270. The prevalence of HLA-B*5801 carriers is 22.3, 7.3 and 3.5% among Singaporean Chinese, Malays and Indians, respectively. These estimates are based on publicly available allele frequencies and Hardy–Weinberg 2009 Equilibrium [Pillai NE et al. Predicting HLA alleles from high-resolution SNP data in three southeast Asian populations. Hum Mol Genet 2014;23:4443-51 and Singapore Pharmacogenomics Portal. www.statgen.nus.edu.sg), resulting in an ethnicity-weighted prevalence of 18.5%. The prevalence of allopurinol-induced SJS/TEN in Singapore was assumed to be the same as Taiwan at 0.2% because of the predominantly Chinese ethnic populations (Tassaneeyakul W et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens–Johnson syndrome and toxic epidermal necrolysis in a Thai population. Pharmacogenet Genomics 2009;19:704-9). The reported sensitivity and specificity of the HLA-B*5801 test is 100 and 85%, respectively (Hung S-I et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci USA 2005;102:4134-9). Therefore, the positive and negative predictive value are estimated to be 1.52 and 100%, respectively (Tassaneeyakul 2009). The incidence rates of death due to SJS, SJS/TEN and TEN (respectively 5%, 15% and 30%) were derived from literature (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).

Different organizations have reached different recommendations on genetic testing. The American College of Rheumatology recommends HLA-B*5801 genotyping as a risk management measure for at-risk populations. The European Medicines Agency cautions against routine HLA-B*5801 genotyping. The Taiwan FDA has issued a notice that HLA-B*5801 should be considered prior to allopurinol treatment, but testing is not mandatory [Taiwan Food and Drug Administration. Drug Safety News (2009). www.fda.gov.twtc].

- Park DJ et al. Cost-effectiveness analysis of HLA-B5801 genotyping in the treatment of gout patients with chronic renal insufficiency in Korea. Arthritis Care Res 2015;67:280-7. PubMed PMID: 25047754.

Compared with allopurinol for all, HLA-B*5801 guided therapy for Korean gout patients with chronic renal insufficiency is less costly and more effective. The genotype guided therapy consisted of febuxostat for patients with HLA-B*5801 and allopurinol for patients without HLA-B*5801. The total expected cost and probability of continuation of gout treatment without severe cutaneous adverse events for the conventional and HLA-B*5801 screening strategies were $1,193 and 97.8% and $1,055 and 100%, respectively. The results were robust according to sensitivity analyses. Until the prevalence of HLA-B*5801 decreased to 3.81%, the genotype guided therapy was less costly than allopurinol for all.

Costs were evaluated from the perspective of a national health payer. Direct medical costs were calculated for a period of 12 months. The calculation was based on a price of 300 mg allopurinol of $ 0.24, a price of 80 mg febuxostat of $ 0.52, a price of treatment of non-fatal and fatal severe cutaneous adverse events of respectively $ 7,429 and $ 14,363, and genotyping costs of $ 62.70. Direct medical costs were obtained from real patients with severe cutaneous adverse events from 2 tertiary hospitals. The prevalence of HLA-B*5801 (12.2%) was derived from Lee 2005 (Lee KW et al. Allelic and haplotypic diversity of HLA-A, -B, -C, -DRB1, and -DQB1 genes in the Korean population. Tissue Antigens 2005;65:437-47). The incidence rate of allopurinol-induced severe cutaneous adverse events in patients with HLA-B*5801 (18%) was derived from Jung 2011 (Jung JW et al. HLA-B58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency. Nephrol Dial Transplant 2011;26:3567-72) and the death rate from severe cutaneous adverse events (27%) from Singer 1986 and Khanna 2012 (Singer JZ et al. The allopurinol hypersensitivity syndrome: unnecessary morbidity and mortality. Arthritis Rheum 1986;29:82-7 and Khanna D et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and anti-inflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res 2012;64:1447–61). The assumed death rate closely matched the experience of the authors: among cases at 2 tertiary hospitals, 5 (23.8%) of 21 patients with allopurinol-induced severe cutaneous adverse events died.

Sensitivity analyses were performed by varying the input parameters. When the prevalence of HLA-B*5801 was assumed to be 5.7% according to Kim 2013 (Kim SC et al. Severe cutaneous reactions requiring hospitalization in allopurinol initiators: a population-based cohort study. Arthritis Care Res 2013;65:578-84), even though the incidence of severe cutaneous adverse events following conventional allopurinol treatment was reduced from 2.19% to 1.03%, treatment informed by HLA-B*5801 genotyping was still less costly and more effective. The total expected costs of allopurinol for all and genotype guided treatment were $ 1,083 and $ 1,053, respectively.

When the incidence of severe cutaneous adverse events in patients with HLA-B*5801 was halved (9%), the costs of genotype guided treatment were still $ 24.90 less than the costs of allopurinol for all. In this case, the genotype guided treatment would be less costly unless the prevalence of HLA-B*5801 was 7.75% or lower.

When the death rate from severe cutaneous adverse events was assumed to be 6% according to Stamp 2012 (Stamp LK et al. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. Arthritis Rheum 2012;64:2529–36), the costs of genotype guided treatment were still $ 105 less than the costs of allopurinol for all. In this case, the genotype guided treatment would be less costly unless the prevalence of HLA-B*5801 was 4.53% or lower.

When the costs of treatment of non-fatal and fatal severe cutaneous adverse events were decreased to $ 4,478 and $ 8,956, respectively, the genotype guided treatment would be less costly unless the prevalence of HLA-B*5801 was below 6.5%.

With all of the above scenarios simultaneously (5.7% prevalence of HLA-B*5801, 9% incidence of severe cutaneous adverse events in patients with HLA-B*5801, 6% death rate from severe cutaneous adverse events, and costs of $ 4,478 and $ 8,956 for treatment of non-fatal and fatal severe cutaneous adverse events, genotype guided treatment was not less costly anymore (costs $39.90 more than for allopurinol for all). In this circumstance, to make genotype guided therapy less costly again, the prevalence of HLA-B*5801 would have to be at least 15.7%, or genotyping costs would need to drop below $22.70.

If the costs of genotyping were halved ($ 31.30), the costs saved by the genotype guided treatment compared to allopurinol for all would increase from $ 138 to $ 169.

- Saokaew S et al. Cost-effectiveness analysis of HLA-B*5801 testing in preventing allopurinol-induced SJS/TEN in Thai population. PLoS One 2014;9:e94294. PubMed PMID: 24732692.

Compared with allopurinol for all, HLA-B*5801 guided therapy for Thai gout patients of 30 years of age with normal renal function is cost-effective (costs of 156,937.04 Thai Baht = US$ 5,062 per QALY gained). This is lower than the willingness-to-pay threshold of 1.2 times the Gross National Income per capita (160,000 Thai Baht = US$ 5,161). The genotype guided therapy consisted of probenecid for patients with HLA-B*5801 and allopurinol for patients without HLA-B*5801. The cost of gout management, incidence of SJS/TEN, case fatality rate of SJS/TEN, and cost of genetic testing are considered very influential parameters on the cost-effectiveness value of genotype guided therapy.

Costs were evaluated from a societal perspective. Lifelong direct medical and direct non-medical costs were calculated. For allopurinol for all patients, the calculated costs per patient were 228,806.8089 Thai Baht (THB) and the calculated QALYs 16.98360. For genotype guided therapy, the calculated costs per patient were 229,730.72791 THB and the calculated QALYs 16.98949. The calculation was based on a life expectancy of Thai (at 30 years old) of 42.7 year, a price of allopurinol of 411.99 THB/year, a price of probenecid of 1,277.50 THB/year, a price of SJS/TEN treatment of 15,440.275 THB/year, a price of gout treatment of 7,512 THB/year, a price of treatment of long-term complications from SJS/TEN of 4,043.90 THB/year and genotyping costs of 1,000 THB. The association between HLA-B*5801 and allopurinol-induced SJS/TEN in the Thai population (OR = 348.33) was derived from Somkrua 2011. The sensitivity and specificity (both 1.000) were derived from the Department of Medical Sciences, Thailand. The prevalence of HLA-B*5801 (15%) was derived from Romphruk 2010 and Gonzalez-Galarza 2011 (Romphruk AV et al. HLA class I and II alleles and haplotypes in ethnic Northeast Thais. Tissue Antigens 2010;75:701-11 and Gonzalez-Galarza FF et al. Allele frequency net: a database and online repository for immune gene frequencies in worldwide populations. Nucleic Acid Research 2011;39:D913-9. http://www.allelefrequencies.net/Accessed 14 July 2013). The incidence of allopurinol-induced SJS/TEN (0.16%) and the death rate from SJS/TEN (11.34%) were derived from Limkobpaiboon 2010 (Limkobpaiboon S et al. Prevalence and mortality rate of severe cutaneous adverse reactions in Siriraj hospital. Chula Med J 2010;54:467-78). The rate of long-term complications from SJS/TEN (37.6%) was derived from Yip 2007 (Yip LW et al. Ocular manifestations and complications of Stevens-Johnson syndrome and toxic epidermal necrolysis: an Asian series. Allergy 2007;62:527-31).
Sensitivity analyses were performed by varying the input parameters. In the probabilistic sensitivity analysis (i.e. varying all parameters simultaneously), genotype guided therapy increased both costs and QALY in all iterations. At the threshold of 160,000 THB (US$ 5,161) per QALY gained, 49.4% of the iterations were cost-effective.
The uncertainty in medical care cost of gout management has the largest influence on the calculated costs per QALY gained. When cost of gout management was varied from 149 to 474,254 THB (US$ 4.8 to 15,298), the costs were 151,594 to 495,645 THB (US$ 4,890 to 15,989) per QALY gained, respectively. Besides, incidence of allopurinol-induced SJS/TEN, discount rate, and probability of death with SJS/TEN in Thai population also have a large influence on the costs per QALY gained. An additional factor with influence is the cost of genetic testing.
When benzbromarone (median cost/tablet 6.95 THB or US$ 0.224) was used as alternative drug instead of probenecid (median cost/tablet 1.75 THB or US$ 0.056), the costs were shifted from 156,937 to 156,989 THB (US$ 5,062 to 5,064) per QALY gained. Thus genotype guided therapy was also cost-effective if benzbromarone was used as an alternative.
When the age at start was varied from 25 to 50 years old, the costs were changed from 148,708 to 221,803 THB (US$ 4,797 to 7,155) per QALY gained.

- Existing guidelines:
  - Saito Y et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. Clin Pharmacol Ther 2016;99:36-7. PubMed PMID: 26094938 and
    Hershfield MS et al. Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing. Clin Pharmacol Ther 2013;93:153-8. PubMed PMID: 23232549.
    *HLA-B*5801*
    CPIC indicates that there is substantial evidence linking HLA-B*5801 with the risk of allopurinol-induced severe cutaneous adverse events. As references they mention 26 primary studies, most of which have been integrated in the meta-analyses summarised in our risk analysis and/or have been included in our risk analysis separately. They indicate that the quality of evidence is high in most of these studies.
    CPIC describes six of these studies and one meta-analysis in more detail. Five of these studies were included in all four meta-analyses in our risk analysis and the sixth in the two most recent meta-analyses. In addition, one study and the meta-analysis were included in our risk analysis separately. CPIC indicates that the association of HLA-B*5801 with allopurinol-induced severe cutaneous adverse events was first identified in the Taiwan Han-Chinese population (Hung SI et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci USA 2005;102,4134-9). HLA-B*5801 was present in 100% (51/51) of the patients with allopurinol-induced severe cutaneous adverse events, as compared with 15% (20/135) of allopurinol-tolerant controls and 20% (19/93) of the population controls. This strong association was replicated in a Thai population, in which 100% (27/27) of the patients with allopurinol-induced severe cutaneous adverse events carried the allele and only 13% (7/54) of the allopurinol-tolerant controls (Tassaneeyakul W et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. Pharmacogenet Genomics 2009;19:704-9). A similar but more modest association was observed in three other populations. 80% (4/5) of Korean cases with severe cutaneous adverse events carried the allele versus 12% (59/485) of healthy Korean controls (Kang HR et al. Positive and negative associations of HLA class I alleles with allopurinol-induced SCARs in Koreans. Pharmacogenet Genomics 2011;21:303-7). In a Japanese population, 56% (10/18) of the cases with allopurinol-induced severe cutaneous adverse events had HLA-B*5801 as against 0.61% (6/493) of healthy controls (Tohkin M et al. A whole-genome association study of major determinants for allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. Pharmacogenomics J 2013;13:60-9 and Kaniwa N et al. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. Pharmacogenomics 2008;9:1617-22). A

European study identified HLA-B*5801 in 55% (15/27) of patients with allopurinol-induced severe cutaneous adverse events, whereas only 1.5% (18/1,822) of the controls tested positive for the allele (Lonjou 2008). One meta-analysis that consolidated all the published studies gave the odds ratios for allopurinol-induced severe cutaneous adverse events in HLA-B*5801 carriers as 73 and 165 for studies using healthy controls and allopurinol-tolerant controls, respectively (Zineh 2011).
CPIC indicates that the Taiwan Department of Health has added the recommendation to test for HLA-B*5801 before the use of allopurinol to the allopurinol label. The Japanese label contains the precaution describing the association of HLA-B*5801 and allopurinol-induced severe cutaneous adverse events citing three references (Kaniwa 2008, Hung 2005 and Lonjou 2008). In addition, CPIC indicates that, given the high specificity for allopurinol-induced severe cutaneous adverse events, allopurinol should not be prescribed to patients who have tested positive for HLA-B*5801. Alternative medication should be considered for these patients to avoid the risk of developing severe cutaneous adverse events. CPIC classifies this recommendation as strong. For patients who have tested negative, allopurinol may be prescribed as usual. However, testing negative for HLA-B*5801 does not totally eliminate the possibility of developing severe cutaneous adverse events, especially in the European population.
CPIC indicates that several clinical factors have been reported to be associated with an increased risk for allopurinol hypersensitivity. Renal dysfunction is the most significant non-genetic factor, and patients with renal insufficiency were four times more likely to develop adverse events than those with normal renal function (Hung 2005). In addition, in patients with severe cutaneous adverse events and renal impairment, oxypurinol concentrations remain higher after drug cessation and this has been associated with higher mortality (Chung WH et al. Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin. Ann Rheum Dis 2015;74: 2157-64). The risk of allopurinol-induced hypersensitivity is also reported to increase with the concomitant use of ampicillin or amoxicillin.
CPIC indicates that, in addition to severe cutaneous adverse events, allopurinol therapy is also associated with a 2–3% incidence of less severe rashes unassociated with systemic symptoms or organ damage. Food and Drug Administration guidelines recommend discontinuing allopurinol if a rash develops. Considering the possible alternatives, CPIC indicates that probenecid is often less effective than allopurinol, particularly in patients with renal insufficiency, and benzbromarone is not an approved drug in many countries. This has prompted attempts to induce tolerance to allopurinol by rechallenge with gradual escalation of low doses as tolerated. This unreliable approach has not been widely accepted, and its use may decline because alternative urate-lowering therapies are now available. Febuxostat is a nonpurine xanthine oxidase inhibitor that is primarily metabolized in the liver to inactive glucuronide and excreted into the urine and bile. Therefore, mild to moderate renal impairment might have little impact on the pharmacokinetics of febuxostat. It was reported to be tolerated in 12 of 13 patients with a history of severe allopurinol hypersensitivity (Chohan S. Safety and efficacy of febuxostat treatment in subjects with gout and severe allopurinol adverse reactions. J. Rheumatol 2011;38:1957-9). In 2010, the Food and Drug Administration approved pegloticase, a PEGylated urate oxidase, as an orphan drug for treating patients with refractory chronic gout who had an inadequate response to, or were intolerant of, other urate-lowering drugs (Sundy JS et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. JAMA 2011;306:711-20). Newer urate-lowering drugs are in clinical trials.
CPIC mentions potential benefits and risks of HLA-B*5801 testing. Given the high negative predictive value of the allele, especially in patients of Asian descent (>99%), HLA-B*5801 testing could significantly reduce the incidence and risk for allopurinol-associated severe cutaneous adverse events. The positive predictive value for HLA-B*5801 is ~1.5% and the negative predictive value is 100% (based on the data from the Han-Chinese and Thai populations) (Tassaneeyakul 2009). Therefore, a significant number of patients carrying the allele will not develop severe cutaneous adverse events when they receive allopurinol treatment. New genetic factors may be identified in the future to differentiate the HLA-B*5801 carriers who are or are not likely to develop severe cutaneous adverse events. However, further study is warranted on the development of severe cutaneous adverse events in European populations.
CPIC indicates that HLA-B*5801 predicts only allopurinol-induced severe cutaneous adverse events, not other adverse events (such as mild skin rash) that a patient might experience during allopurinol treatment. The marker also does not predict the efficacy of treatment with allopurinol. Regardless of the genotyping results, physicians should monitor patients closely.
CPIC indicates that although none of the evidence linking HLA-B*5801 to allopurinol hypersensitivity was conducted in children, there is no reason to suspect that children positive for HLA-B*5801 would be at less risk of allopurinol hypersensitivity reactions than adults positive for HLA-B*5801.
CPIC provides the following recommendation for HLA-B*5801-positive patients:
- allopurinol is contraindicated
The recommendation above is still the same after the last update on 6-12-2015 on the PharmGKB-site.
*HLA-A*3303 and HLA-C*0302*
CPIC indicates that 7 studies showed associations for HLA-A*3303 and 5 studies for HLA-C*0302. However, the strength of the evidence for HLA-A*3303 and HLA-C*0302 did not warrant inclusion in the guideline. This association so far has only been reported in a very few studies, some of which simply report association with the HLA-A*33 or HLA-Cw3 allele. In addition, these two alleles also show high linkage disequilibrium with HLA-B*5801 (Kang HR et al. Positive and negative associations of HLA class I alleles with allopurinol-induced SCARs in Koreans. Pharmacogenet Genomics 2011;21:303-7). Having evaluated the evidence, CPIC

feels therapeutic recommendations for allopurinol based upon presence of the HLA-A*33:03 or HLA-C*03:02 allele cannot be made at this time.

- European Medicine Agency CFMPFHU, Pharmacovigilance Working Party. Allopurinol: risk of skin reactions associated with HLA-B*5801 allele. Pharmacovigilance Working Party (PhVWP) monthly report on safety concerns, guidelines and general matters, July 2012. EMA/CHMP/PhVWP/438980/2012. www.ema.europa.eu

  Allopurinol-induced serious cutaneous adverse reactions (SCAR), including Steven Johnson's syndrome (SJS) and toxic epidermal necrolysis (TEN), are associated with a genetic marker, the HLA-B*5801 allele. The sensitivity of prior testing for HLA-B*5801 may be as low as 50% in European populations. This suggests that potentially half of European patients that do develop SCAR will not be identified by prior testing. Although the sensitivity of prior testing is likely to be higher in other populations, particularly the Han Chinese, there is a lack of suitable alternative therapies to allopurinol. Furthermore, the clinical utility of testing for this allele prior to treatment with allopurinol is not proven in any population.

  Therefore, the recommendation at present is that:

  - The use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established.
  - Routine testing for HLA-B*5801 is not recommended in any patients. If the patient is a known carrier of HLA-B*5801, the use of allopurinol may be considered if the benefits are thought to exceed risks. Extra vigilance for signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately at the first appearance of symptoms.

  The CHMP Pharmacovigilance Working Party (PhVWP) reviewed pharmacogenetic study findings regarding allopurinol-induced severe cutaneous (i.e. skin) adverse reactions (SCAR) and finalised their conclusions for updating the product information of allopurinol-containing medicinal products authorised in the EU (see Annex 1 for the Summary Assessment Report).

  The PhVWP informed the CMDh accordingly. For the final wording to be included in the product information, i.e. the summaries of product characteristics and package leaflets, as well as practical information on implementation, interested readers are advised to consult the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

- Khanna D et al. 2012 American college of rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res 2012;64:1431-46.

  One of the core recommendations in the use of allopurinol:

  Prior to initiation, consider rapid polymerase chain reaction-based HLA–B*5801 screening as a risk management component in selected patients, specifically in subpopulations at higher risk for severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 or worse chronic kidney disease, and Han Chinese and Thai irrespective of renal function; evidence A).

  In these subpopulations both the HLA-B*5801 allele frequency is elevated and the HLA-B*5801-positive subjects have a very high hazard ratio ("high risk") for severe allopurinol hypersensitivity reaction.

  The task force panel (TFP) weighed the rapidly emerging area of pharmacogenetics to screen for severe allopurinol hypersensitivity reaction (SCAR) (Zineh I et al. Allopurinol pharmacogenetics: assessment of potential clinical usefulness. Pharmacogenomics 2011;12:1741–9; Somkrua 2011 and Lee MH et al. Initiating allopurinol therapy: do we need to know the patient's HLA status? Intern Med J 2011;42:411-6), and recommended that, prior to initiation of allopurinol, HLA-B*5801 testing should be considered in select patient subpopulations at an elevated risk for SCAR (evidence A). Those with HLA-B*5801 and of Korean descent with stage 3 or worse chronic kidney disease (HLA-B*5801 allele frequency ~12%), or of Han Chinese or Thai extraction irrespective of renal function (HLA–B*5801 allele frequency ~6–8%), have been highlighted in the literature as prime examples of subjects at high risk for SCAR, marked by HLA-B*5801 hazard ratios of several hundred (Jung JW et al. HLA-B58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency. Nephrol Dial Transplant 2011;26:3567-72; Hung SI et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci USA 2005;102: 4134-9 and Tassaneeyakul W et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. Pharmacogenet Genomics 2009;19:704–9). Such high-risk individuals were recommended to be prescribed an alternative to allopurinol if HLA–B*5801 positive (evidence A).

  The TFP recommended that the HLA-B*5801 screening be done by the rapid, widely available polymerase chain reaction (PCR)-based approach (evidence A) that, in only ~10% of tests, requires more cumbersome follow-up HLA-B*5801 sequencing for inconclusive results. Significantly, the TFP did not recommend universal HLA-B*5801 allopurinol screening. Current evidence informing this TFP decision included that whites with an HLA-B*5801 prevalence of ~2% had a substantially lower HLA-B*5801 hazard ratio and negative predictive value of the test than in the aforementioned Asian subpopulations (Zineh 2011; Lee 2011 and Lonjou 2008). The TFP also made the novel recommendation that rapid PCR-based HLA-B*5801 screening should be considered as a risk management component in subpopulations where both the HLA-B*5801 allele frequency is elevated and the HLA-B*5801-positive subjects have a very high hazard ratio ("high risk") for severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 [or worse] chronic kidney disease and all those of Han Chinese and Thai descent). It is anticipated that additional high-risk subpopulations for SCAR will be identified in future studies.

We note that a recent single technology appraisal with cost analysis done by an independent evidence review group of the National Institute for Health and Clinical Excellence concluded that febuxostat should be recommended for urate lowering therapy in gout only in patients with contraindications or intolerance to allopurinol (Stevenson M et al. Febuxostat for the management of hyperuricaemia in patients with gout: a NICE single technology appraisal. Pharmacoeconomics 2011;29:133-40). Conversely, PCR-based HLA-B*5801 pharmacogenetics screening for allopurinol is a one-time test and relatively inexpensive, but raises new questions about the added costs to gout management, particularly for populations where the risk of SCAR is low (Zineh 2011; Somkrua 2011 and Lee 2011).

Date of the literature search: 15 December 2020.

	Genotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working group decision	HLA-B*5801	4 F	yes	yes	7 June 2021

Mechanism:
Although the mechanism of hypersensitivity for allopurinol is not exactly known, experimental data suggests the mechanism below.
A cellular immune reaction against body cells is induced if peptides derived from proteins within these body cells bind to specific HLA-proteins, are transported to the cell surface and are 'recognized' as foreign by specific immune cell proteins (T-cell receptors). The allopurinol metabolite oxypurinol binds to either specific HLA-proteins, the cellular proteins or derived peptides or specific T-cell receptors, thus inducing an interaction between a HLA-peptide complex and a T-cell receptor, resulting in a cellular immune reaction against body cells.
Impaired kidney function diminishes the oxypurinol clearance and increases the risk of allopurinol induced cutaneous adverse events.

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**	
		Asian, not Japanese, or African	**other ethnicity**
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+	8+	6+
Corresponding Clinical Implication Score:		Essential	Essential
Score after taking additional considerations into account:		Beneficial	Beneficial