Allopurinol has a long-established role in the management of hyperuricaemia and gout. However, allopurinol can also cause a hypersensitivity reaction that varies in severity from a mild rash to a severe cutaneous adverse reaction (SCAR), which includes Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and systemic eosinophilia. SCAR typically occurs within two months of commencing treatment with allopurinol. The incidence of SCAR is between 1:250 and 1:1,000 in patients commencing therapy with allopurinol. The mortality rate is up to 25%. Clinical Pharmacogenetics Implementation Consortium (CPIC) has summarised the evidence from the published literature and developed peer-reviewed guidelines for allopurinol use based on HLA-B genotype.

### Association of allopurinol SCAR and an HLA variant

The risk of allopurinol-induced SCAR is associated with the presence of a specific HLA variant, HLA-B*5801. The frequency of this variant varies in different populations, being highest (10-20%) in people of Chinese (Han), Korean or Thai ancestry. Allopurinol-induced SCAR is more common in these populations. The variant, and the frequency of allopurinol-induced SCAR, is less common in other populations.

The HLA-B*5801 variant is strongly associated with allopurinol-induced SCAR, but it is not the only factor. In at-risk Asian populations, most of the patients with allopurinol-induced SCAR have the HLA-B*5801 variant. However, in European populations, only half of those with allopurinol-induced SCAR have that HLA variant. Screening patients for the presence of the HLA-B*5801 variant prior to prescribing can reduce the incidence of allopurinol-induced SCAR in patients with Chinese (Han), Korean, or Thai ancestry, but may be of less benefit in other patients.

### Evidence of the utility of screening before prescribing

The clinical utility of screening for the HLA-B*5801 variant prior to prescribing allopurinol has been studied in Taiwan (which has a predominantly Chinese (Han) population). Because of the recognised association of the HLA variant with allopurinol-induced SCAR, this was a non-randomised cohort study rather than a randomised blinded study.

When screening for the HLA-B*5801 variant was introduced, 354 patients (20%) had the variant and were prescribed a variety of medications other than allopurinol. The remaining 2,173 patients (80%) lacked the variant and were prescribed allopurinol. Once screening was introduced, there were no instances of allopurinol-induced SCAR. The reduction in incidence of SCAR among those with the HLA-B*5801 variant treated with other medications was highly significant (p<0.005).

### Screening for susceptibility to allopurinol-induced SCAR

Testing for the HLA-B*5801 variant is readily available.

The American College of Rheumatology recommends that all Chinese (Han) and Thai patients, and Korean patients with impaired renal function, be screened for presence of the HLA-B*5801 variant prior to treatment with allopurinol. Note that a person need only have such ancestry on one side of the family to have an increased chance of having this HLA variant.

Patients who have either one or two copies of the HLA-B*5801 variant should avoid allopurinol.