INTER-SOCIETY COORDINATING COMMITTEE, USE CASE WORKGROUP

I. **Specialty/Professional Society**: Pharmacology, Neurology, Rheumatology, Dermatology, Infectious Diseases

II. **Type of Use Case**: Genomic-based therapeutics

a. Pharmacogenomic

III. **Title**: HLA-B alleles and adverse events related to use of carbamazepine and allopurinol

IV. **Clinical Scenarios**:

Case 1

A 57 year old female of Asian descent was admitted to a hospital for peripheral nerve pain. Her physician ordered a DNA-sequencing based test for HLA and she was found to be positive for the *HLA-B*15:02* allele. She was discharged with a prescription for carbamazepine by a second physician who was not aware of the HLA genotyping result. Within one day of taking the medication, she developed a rash. She continued the medication and over 5 days the rash worsened significantly, with blistering, and she was admitted to the hospital with the diagnosis of Stevens Johnson syndrome – Toxic Epidermal Necrolysis (SJS-TEN). Despite care in a burn unit, the patient died within 2 days of admission.

Case 2

A 62 year old male of Southeast Asian descent was started on allopurinol for gout. Approximately 1 week after starting therapy, the patient developed fever, mild sore throat, and excessive tearing from his eyes. The following day he developed a dusky red rash on his face and pre-sternal region and returned to his physician. The allopurinol was discontinued immediately and HLA testing ordered. The patient was found to be positive for the *HLA-B*58:01* allele and was switched to colchicine for treatment of his gout.

V. **Relevant Genomic Information**: Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with carbamazepine, allopurinol, sulfonamides, and other drugs. These severe adverse drug reactions include cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) as illustrated in the clinical scenarios. In countries with a primarily Caucasian population, the incidence is 1-6 per 10,000 new users. The rate approaches 10 times higher in Asian and Asian Indian populations. Individuals who are positive for the *HLA-B*15:02* allele appear to be at high risk for developing SJS-TEN to carbamazepine, and people who are positive for the *HLA-B*58:01* allele are at high risk of SJS-TEN after allopurinol therapy. The *HLA-B*15:02* allele is rare outside of specific Asian countries; the *HLA-B*58:01* allele is common in people of Asian descent, but is also present in those of European and African descent.

The FDA has placed a black box warning recommending that patients of Asian ethnicity be screened for *HLA-B*15:02* prior to initiation of carbamazepine, and the American College of Rheumatology recommends testing for the *HLA-B*58:01* allele in selected subpopulations with elevated risk for allopurinol hypersensitivity syndrome (individuals of Korean descent

with stage 3 or worse chronic kidney disease, and those of Han-Chinese or Thai descent) prior to initiation of the drug.

Currently there are no recommendations for population-based testing for high-risk HLA-B alleles beyond those identified high-prevalence populations, but as the cost of testing is reduced or other high-risk alleles are identified in additional populations, this situation might change.

VI. **Recommended Clinical Action**: In patients of Asian descent, screening for *HLA-B*15:02* should be performed prior to starting carbamazepine and *HLA-B*58:01* screening should be considered before starting allopurinol. If one or more high-risk alleles are present, an alternative medication is indicated unless the benefits of carbamazepine or allopurinol clearly outweigh the risks. Because of an increased risk of SJS-TEN in patients with *HLA-B*15:02* exposed to phenytoin, this medication should be avoided when considering a substitute for carbamazepine or other medications. Note also that abacavir, used to treat human immunodeficiency virus infection, can also cause immune-mediated hypersensitivity reactions in individuals who carry one or more HLA-B*57:01 alleles.

Case 1 represents a preventable death, as poor communication amongst medical personnel resulted in a patient with a known *HLA-B*15:02* allele being prescribed carbamazepine. Electronic Health Record alerts and the use of medical alert bracelets might have prevented this outcome. In addition, patients can be enlisted in advocating for their own care, as if they had a medication allergy to be urgently communicated to all health care providers. Consumer-friendly information to support patient education is available from Genetics Home Reference and MedLinePlus (see Section IX.)

VII. **Family Implications**: Consideration should be given to offering testing to close relatives of those positive for one of the high-risk alleles.

VIII. **Supporting Evidence**: Guidelines from the Clinical Pharmacogenetics Implementation Consortium, FDA labels, and prescribing information from PharmGKB (see Section IX.)

IX. References and Resources

a. PharmGKB prescribing information for carbamazepine. http://www.pharmgkb.org/drug/PA448785
b. PharmGKB prescribing information for allopurinol. http://www.pharmgkb.org/guideline/PA166105003
c. FDA Label, carbamazepine. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fbca2152-0022-47a5-a1ea-58950b45bcbf
d. FDA Label, allopurinol. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=19a138b8-d225-03e6-f762-abe71560204b
e. Lim KS. et al. (2008) Association of HLA-B*1502 allele and carbamazepine-induced severe adverse cutaneous drug reaction among Asians-A review. Neurol Asia. 13:15-21. (http://neurologyasia.org/articles/20081_015.pdf)
f. Leckband SG et al. Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and carbamazepine dosing. Clin Pharmacol Ther. 2013 Sep;94(3):324-8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3748365/

g. Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3564416/
h. Khanna D., et al. 2012 American College of Rheumatology Guidelines for Management of Gout Part I: Systematic Non-pharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3683400/
i. Carbamazepine Therapy and HLA Genotypes. Medical Genetics Summaries. https://www.ncbi.nlm.nih.gov/books/NBK321445/
j. Allopurinol Therapy and HLA-B*58:01 Genotype. Medical Genetics Summaries. https://www.ncbi.nlm.nih.gov/books/NBK127547/
k. Phenytoin Therapy and HLA-B*15:02 and CYP2C9 Genotypes. Medical Genetics Summaries. https://www.ncbi.nlm.nih.gov/books/NBK385287/
l. Abacavir Therapy and HLA-B*57:01 Genotype. Medical Genetics Summaries. https://www.ncbi.nlm.nih.gov/books/NBK315783/
NIH Genetic Testing Registry.
Carbamazepine response: https://www.ncbi.nlm.nih.gov/gtr/conditions/CN077964/
Allopurinol response: https://www.ncbi.nlm.nih.gov/gtr/conditions/CN160494/
m. Consumer resources.
Genetics Home Reference. https://ghr.nlm.nih.gov/condition/stevens-johnson-syndrome-toxic-epidermal-necrolysis
MedLinePlus. https://medlineplus.gov/druginfo/meds/a682237.html