Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Human Leukocyte Antigen B (HLA-B) Genotype and Allopurinol Dosing: 2015 Update

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The Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *HLA-B*58:01* Genotype and Allopurinol Dosing was originally published in February 2013. We reviewed the recent literature and concluded that none of the evidence would change the therapeutic recommendations in the original guideline; therefore, the original publication remains clinically current. However, we have updated the Supplemental Material and included additional resources for applying CPIC guidelines into the electronic health record. Up-to-date information can be found at PharmGKB (http://www.pharmgkb.org).

The Clinical Pharmacogenetics Implementation Consortium (CPIC) of the Pharmacogenetics Research Network (http://www.pgrn.org) and the Pharmacogenomics Knowledge Base (PharmGKB, http://www.pharmgkb.org) provides peer-reviewed, evidence-based, freely accessible genotype-based drug guidelines to help clinicians understand how available genetic test results could be used to optimize drug therapy.[1] CPIC guidelines undergo continuous peer review and information that would modify prescribing recommendations pertaining to gene specific alleles and nomenclature are updated periodically on the PharmGKB website. Furthermore, published CPIC guidelines are currently systematically reviewed for updates periodically.

The CPIC Guideline for *HLA-B* Genotype and Allopurinol Dosing was originally published in February 2013.[2] To update this guideline, we conducted a focused review of the literature published between 1966 to October 2014 on *HLA* genotype and allopurinol (see **Supplemental Material** online). Our inclusion criteria for this guideline update also included other *HLA* variants besides *HLA-B*. The *HLA-B*58:01* allele frequency tables (**Supplemental Tables S1 and S2**) have also been updated. The literature review yielded 26 relevant primary studies showing an association between *HLA-B*58:01* and allopurinol severe cutaneous adverse reactions (SCAR) (**Supplemental Table S3**). In addition, 12 studies showed associations for *HLA-A*33:03* (seven studies) or *HLA-C*03:02* (five studies) **(Supplemental Table S3)**. However, the strength of the evidence for *HLA-A*33:03* and *HLA-C*03:02* did not warrant inclusion in this update (please see "Other considerations" in the **Supplementary Materials**). We found no new evidence that would change our original recommendations for *HLA-B*58:01* and allopurinol dosing; therefore, the original guideline publication and recommendation remains current.[2] The 2012 American College of Rheumatology Guidelines for Management of Gout[3] 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

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those of Han-Chinese or Thai descent) prior to initiation of the drug.

All new and updated CPIC guidelines will address dosing in pediatrics. Although none of the evidence linking *HLA-B*58:01* to allopurinol hypersensitivity was conducted in children, there is no reason to suspect that children positive for *HLA-B*58:01* would be at less risk of allopurinol hypersensitivity reactions than adults positive for *HLA-B*58:01*.

CPIC guidelines are designed to help clinicians use genetic information to optimize drug therapy, and to do this effectively, pharmacogenetic information must be incorporated into electronic health records (EHRs) with clinical decision support (CDS).[4–6] To provide additional resources for applying CPIC guidelines into the EHR, CPIC created an informatics working group focused on supporting the adoption of CPIC guidelines within a clinical electronic environment. This guideline provides these clinical implementation resources as part of the **Supplementary Material**, which include workflow diagrams that illustrate the storage of a pharmacogenetic result in an EHR and the design of CDS alerts (**Supplemental Figures S1 and S2**). Tables that correspond to these workflow diagrams are provided that translate genotype test results into an interpreted phenotype (**Supplemental Tables S4–S7**). These tables provide summary genotype/phenotype terms, example text for documentation in the EHR and point-of-care alerts, and cross-references for drug and gene names to widely used terminologies and standardized nomenclature systems.

We recognize that each organization and EHR vendor may have different requirements and preferences for implementing pharmacogenetics within a given electronic environment. The intent of these resources is to synthesize foundational knowledge that provides a common starting point for clinical implementation so that individual organizations do not have to create a similar knowledge base for each new gene/drug pair that is implemented. Future CPIC guidelines and guideline updates will provide similar resources to guide the implementation of gene-drug pairs into the EHR.

DISCLAIMER

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written, and are intended only to assist clinicians in decision-making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the healthcare provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC's guidelines, or for any errors or omissions.

Additional Supporting Information may be found in the online version of this article.

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CONFLICT OF INTEREST

T.E.K. is a stockholder for Personalis Inc. L.K.S. has been a consultant for Astra Zeneca. As of January 2015, E.M.M. is Lead Scientific Curator of Genomics England, Queen Mary University. M.S.H. is a coinventor of Pegloticase (Krystexxa®) and receives royalties from Crealta Pharmaceuticals. The other authors declare no conflicts of interest.

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