Supplemental Material

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

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CPIC Updates

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published in full on the PharmGKB website (www.pharmgkb.org). Relevant information will be periodically reviewed and updated guidelines will be published online.

CPIC Updates in Supplement v2.0:

- **Updated literature review to include publication up to November 2014.**
- **Added new information describing a mechanistic link for severe cutaneous adverse reactions in *HLA*B58:01* population.**
- **Added additional information regarding other HLA variants and implications for allopurinol use.**
- **Added resources to facilitate incorporation of HLA-B pharmacogenetics into an electronic health record with clinical decision support**

Focused Literature Review

We searched the PubMed database (1966 to October 2014) for keywords (HLA OR HLA-B OR HLA-B58 OR HLA-B*5801) AND (allopurinol). Using these search terms, 77 publications were identified. In addition, studies annotated in PharmGKB (http://www.pharmgkb.org) were identified. Study inclusion criteria included publications that included analyses of the effect of *HLA* alleles on clinical outcomes of allopurinol use, and non-English manuscripts were excluded. Following application of these inclusion criteria, 26 publications were reviewed and included in the evidence table (Table S3). Associations with other alleles were also collected and the positive associations found in more than one study are represented in Table S3.

To construct an *HLA-B*58:01* minor allele frequency table based on ethnicity, allele

frequency information was obtained from Allele Frequency Net Database (www.allelefrequencies.net), an online repository for HLA allele frequencies from both previously published and unpublished sources. Allele frequency search/classical was carried out for *HLA-B*58:01* (accessed Dec 1st 2014). Reference: Allele frequency net: a database and online repository for immune gene frequencies in worldwide populations (1).

Genetic Test Interpretation and Available Test Options

Commercially available genetic testing options change over time. Additional updated information can be found at:

http://www.pharmgkb.org/resources/forScientificUsers/pharmacogenomic_tests.jsp

Furthermore, the Genetic Testing Registry (GTR) provides a central location for voluntary submission of genetic test information by providers and is available at http://www.ncbi.nlm.nih.gov/gtr/.

The commercial testing for *HLA-B*58:01* appears to be less widespread in availability at present than that of *HLA-B*57:01* (the allele associated with abacavir hypersensitivity). Testing procedures are similar than for *HLA-B*57:01*(2) and may include sequencing or sequence specific priming PCR. Commercially available genetic testing options change over time.

Levels of Evidence linking genotype to phenotype

The evidence summarized in Supplemental Table S4 has been graded using the three-tiered system required by the Clinical Pharmacogenetics Implementation Consortium (3), as modified slightly from Valdes *et al.*(4):

> **High:** Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information

Every effort was made to present evidence from high-quality studies, which provided the framework for the strength of therapeutic recommendations in Table 2.

Strength of Recommendations

The dosing recommendations are simplified to allow rapid interpretation by clinicians, as adapted from the rating scale for evidence-based therapeutic recommendations on the use of allopurinol. As previously described for CPIC guidelines(3), three categories were chosen for recommendations: strong, where "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects"; moderate, in which "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and optional, for recommendations in-between strong and weak where there is room for differences in opinion as to the need for the recommended course of action. CPIC's dosing recommendations are based weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians.

A: Strong recommendation for the statement

B: Moderate recommendation for the statement

C: Optional recommendation for the statement

Drug: Allopurinol

Background

The mechanism by which allopurinol interacts with *HLA-B*58:01* has recently been elucidated. Both Lin and Yun et al demonstrated that oxypurinol, the active metabolite of allopurinol, can preferentially bind to the peptide binding groove of *HLA-B*58:01* and activates T cells in a dose dependent manner (5, 6). The endengous peptide-loaded *HLA-B*58:01* molecule presented oxypurinol to cytotoxic T cells without the involvement of intracellular drug metabolism or antigen-processing pathway, thus suggesting a p-i (direct pharmacological interaction of a drug with immune receptors) concept model.

Delayed clearance of oxypurinol in patients with renal impairment results in higher plasma oxypurinol concentrations. In patients with SCAR and renal impairment oxypurinol concentrations therefore remain higher after drug cessation and this has been associated with higher mortality (7).

Other Considerations

Our literature review included all the HLA gene variants reported to have associations with allopurinol induced SCAR. The majority of associations found were negative or had weak evidence. All positive associations can be viewed at https://www.pharmgkb.org/drug/PA448320?tabview=tab0&subtab=33#tabview=tab0&subtab=33. We only included *HLA-B*58:01* in this recommendation as the

*HLA-B*58:01* allele has high effect size (odds ratio) and the association was observed in multiple populations. Other HLA alleles, *HLA-A*33:03* and *HLA-C*03:02*, have also shown associations with allopurinol induced SCAR (Supplemental Table S3). However, 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*58:01*(8). Having evaluated the evidence, we feel 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.

At the time of submission, the drug labeling has been updated in Taiwan to include this information (http://www.tmuh.org.tw/tmuh_web/Pharmacy/pdf_medsecurity/98-030.pdf) (Please note, the link is in Chinese), and recommends testing for the *HLA-B*58:01* allele before allopurinol use. To our knowledge, US-FDA-approved drug labeling for allopurinol does not contain information regarding *HLA-B*58:01*. The Japanese label contains the precaution describing that association of *HLA-B*58:01* and allopurinol-induced SCAR citing three references (9-11).

Resources to Incorporate Pharmacogenetics into an EHR with CDS

Use of clinical decision support (CDS) tools within electronic health records (EHRs) can assist clinicians to use genetic information to optimize drug therapy (12-16). Supplementary material provides resources from CPIC to support the adoption of CPIC guidelines within an EHR (17). Based on the capabilities of various EHRs and local preferences, we recognize approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for

incorporating the use of *HLA-B*58:01* genotype results to guide the use of allopurinol in any EHR.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. First, pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (18). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient summary section; these phenotypes are best stored in the EHR at the "person level" rather than at the date-centric "encounter level". Second, results should be entered as standardized and discrete terms to facilitate using them to provide point of care CDS (19, 20). Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. Point-of-care CDS should be designed to effectively remind clinicians of prescribing implications at any time after the test result is entered into the EHR. Guidance to achieve these objectives is provided in diagrams that illustrate how *HLA-B*58:01* pharmacogenetic test results could be entered into an EHR (**Supplemental Figure S1**) and be used for point-of-care CDS (**Supplemental Figure S2**). **Supplemental Tables S4** and **S5** provide a cross-reference to widely used nomenclature systems for the drug and the gene, respectively.

To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Table 1, main manuscript**). **Supplemental Table S6** further translates

results into a coded diplotype/phenotype summary, priority result notification, and sample interpretative result text. The result tables provide summary genotype/phenotype terms, example text for documentation in the EHR and point-of-care alerts. Finally, sample point-of-care alert text that corresponds to the workflow described in **Supplemental Figure S2** is provided in **Supplemental Table S7**.

Supplemental Table S1. Frequencies of alleles[1] in major race/ethnic groups[2]

Population Group[2]	Total sample size	Range of HLA-B*5801 carrier frequency (%)
American Indian or Alaska Native	58,106	0.0119
Asian	552,300	0.0532
Black or African American	484, 608	0.0385
White	1421,482	0.0080
Hispanic or Latino	527,027	0.0135
Native Hawaiian or Other Pacific Islander	11,499	0.0145

[1] Range of allele frequencies are reported based on the allele frequencies from Allele Frequencies.net.

[2]OMB Racial/ethnic category group designations corresponding to the populations indicated in Supplemental Table S2, and are mapped to the ethnic origins provided by Allele Frequencies.net. Frequencies were calculated for each group.

Supplemental Table S2. Detailed table of *HLA-B*5801* alleles in defined ethnic groups[1]

OMB Racial/ethnic category	Population	*HLA-B*58:01* Allele Frequency	Sample Size
American Indian or Alaska Native	Guatemala Mayan	0.007	132
American Indian or Alaska Native	Mexico Oaxaca Mixtec	0	103
American Indian or Alaska Native	US NMDP Alaska Native or Aleut	0.006	1,376
American Indian or Alaska Native	US NMDP American Indian South or Central America	0.01	5,926
American Indian or Alaska Native	US NMDP Caribean Indian	0.026	14,339
American Indian or Alaska Native	US NMDP North American Indian	0.007	35,791
American Indian or Alaska Native	USA Alaska Yupik	0	252
American Indian or Alaska Native	USA North American Native	0.008	187
Asian	China Jiangsu Han	0.071	3,238
Asian	India Andhra Pradesh Golla	0.072	111
Asian	US NMDP South Asian Indian	0.042	185,391
Asian	USA Asian	0.074	358
Asian	USA Asian pop 2	0.0577	1,772
Asian	Indonesia Sundanese and Javanese	0.06	201
Asian	Singapore Riau Malay	0.05	132

Asian	US NMDP Filipino	0.0404	50,614
Asian	China Beijing Shijiazhuang Tianjian Han	0.06	618
Asian	China Bulang	0.004	116
Asian	China Canton Han	0.089	264
Asian	China Guangdong Province Meizhou Han	0.17	100
Asian	China Guangxi Region Maonan	0.042	108
Asian	China Guangzhou	0.085	102
Asian	China Guangzhou Han	0.047	106
Asian	China Guizhou Province Bouyei	0.083	109
Asian	China Guizhou Province Shui	0.015	153
Asian	China Hani	0.027	150
Asian	China Inner Mongolia Region	0.088	102
Asian	China Jiangsu Province Han	0.0714	167
Asian	China North Han	0.029	105
Asian	China Qinghai Province Hui	0.023	110
Asian	China South Han	0.089	284
Asian	China Southwest Dai	0.077	124
Asian	China Tibet Region Tibetan	0.016	158
Asian	China Yunnan Province Bulang	0.004	116
Asian	China Yunnan Province Han	0.074	101
Asian	China Yunnan Province Hani pop 2	0.027	150

Asian	China Yunnan Province Jinuo	0.005	109
Asian	China Yunnan Province Lisu	0.007	111
Asian	China Yunnan Province Nu	0.019	107
Asian	China Yunnan Province Wa	0.017	119
Asian	Germany DKMS - China minority	0.0593	1,282
Asian	Hong Kong Chinese	0.073	569
Asian	Japan Central	0.004	371
Asian	Japan pop 16	0.0058	18,604
Asian	Japan pop 3	0.005	1,018
Asian	Singapore Chinese	0.104	149
Asian	Singapore Thai	0.086	100
Asian	South Korea pop 10	0.0608	4,128
Asian	South Korea pop 3	0.065	485
Asian	South Korea pop 9	0.0608	4,128
Asian	Taiwan Han Chinese	0.106	504
Asian	Taiwan Minnan pop 1	0.088	102
Asian	Taiwan pop 2	0.1	364
Asian	Taiwan pop 3	0.101	212
Asian	Taiwan Tzu Chi Cord Blood Bank	0.098	710
Asian	Thailand	0.077	142
Asian	Thailand Northeast pop 2	0.079	400

Asian	US NMDP Chinese	0.0874	99,672
Asian	US NMDP Japanese	0.0076	24,582
Asian	US NMDP Korean	0.0603	77,584
Asian	US NMDP Southeast Asian	0.0478	27,978
Asian	US NMDP Vietnamese	0.0692	43,540
Asian	Vietnam Hanoi Kinh pop 2	0.065	170
Black or African American	Cameroon Beti	0.037	174
Black or African American	Ghana Ga-Adangbe	0.042	131
Black or African American	Kenya	0.08	144
Black or African American	Kenya Luo	0.07	265
Black or African American	Kenya Nandi	0.1	240
Black or African American	Mali Bandiagara	0.022	138
Black or African American	Senegal NiokholoMandenka	0.069	165
Black or African American	South Africa Black	0.081	200
Black or African American	South Africa Natal Zulu	0.04	100
Black or African American	Uganda Kampala	0.04	161
Black or African American	Uganda Kampala pop 2	0.06	175
Black or African American	US NMDP African	0.042	28,557
Black or African American	US NMDP African American	0.038	416,581
Black or African American	US NMDP Caribean Black	0.041	33,328
Black or African American	USA African American	0.064	252

Black or African American	USA African American Bethesda	0.026	187
Black or African American	USA African American pop 3	0.032	564
Black or African American	USA African American pop 4	0.0351	2,411
Black or African American	USA African American pop 8	0.036	605
Black or African American	Zimbabwe Harare Shona	0.044	230
Hispanic or Latino	US NMDP Caribean Hispanic	0.023	115,374
Hispanic or Latino	US NMDP Hispanic South or Central American	0.0142	146,714
Hispanic or Latino	US NMDP Mexican or Chicano	0.009	261,235
Hispanic or Latino	USA Hispanic	0.011	234
Hispanic or Latino	USA Hispanic pop 2	0.0145	1,999
Hispanic or Latino	USA South Texas Hispanic	0.004	194
Hispanic or Latino	USA Spain	0.02	279
Hispanic or Latino	Mexico City Mestizo pop 2	0.0064	234
Hispanic or Latino	Mexico Guadalajara Mestizo pop 2	0.01	103
Hispanic or Latino	USA Mexican American Mestizo	0.009	553
Hispanic or Latino	Brazil Mixed	0.022	108
Native Hawaiian or Other Pacific Islander	US NMDP Hawaiian or other Pacific Islander	0.0145	11,499
White	Israel Arab Druze	0.015	101
White	Jordan Amman	0.014	146
White	Oman	0.068	118
White	Saudi Arabia Guraiat and Hail	0.046	213

White	Tunisia	0.04	100
White	Tunisia pop 3	0.034	104
White	US NMDP Middle Eastern or North Coast of Africa	0.0173	70,890
White	Australia New South Wales Caucasian	0.049	134
White	Austria	0.008	200
White	Azores Terceira Island	0.012	130
White	Croatia	0.013	150
White	Czech Republic	0.014	106
White	Czech Republic NMDR	0.0069	5,099
White	England North West	0.005	298
White	France Corsica Island	0.045	100
White	France Southeast	0.016	130
White	Georgia Tibilisi	0.014	109
White	Germany DKMS - Austria minority	0.0118	1,698
White	Germany DKMS - Bosnia and Herzegovina minority	0.0097	1,028
White	Germany DKMS - Croatia minority	0.0117	2,057
White	Germany DKMS - France minority	0.0125	1,406
White	Germany DKMS - Greece minority	0.0145	1,894
White	Germany DKMS - Italy minority	0.0198	1,159

White	Germany DKMS - Netherlands minority	0.0073	1,374
White	Germany DKMS - Poland minority	0.0065	20,653
White	Germany DKMS - Portugal minority	0.0162	1,176
White	Germany DKMS - Romania minority	0.0097	1,234
White	Germany DKMS - Spain minority	0.0131	1,107
White	Germany DKMS - Turkey minority	0.018	4,856
White	Germany DKMS - United Kingdom minority	0.0048	1,043
White	Germany pop 6	0.0081	8,862
White	Germany pop 8	0.009	39,689
White	Ireland Northern	0.003	1,000
White	Ireland South	0.004	250
White	Italy pop 5	0.016	975
White	Italy Sardinia pop3	0.064	100
White	Macedonia pop 4	0.009	216
White	Madeira	0.016	185
White	Netherlands Leiden	0.006	1,305
White	Poland	0.01	200
White	Romania	0.013	348
White	Serbia pop 2	0.005	102
White	South Africa Caucasians	0.026	102
White	Spain Gipuzkoa Basque	0	100

White	US NMDP European Caucasian	0.0073	1,242,890
White	USA Caucasian Bethesda	0	307
White	USA Caucasian pop 2	0.011	265
White	USA Caucasian pop 4	0.0102	1,070
White	USA Eastern European	0.008	558
White	USA European American pop 2	0.009	1,245
White	USA Italian	0.016	273
White	USA Philadelphia Caucasian	0.019	141
White	USA San Antonio Caucasian	0.003	222
White	USA San Francisco Caucasian	0.014	220
White	Wales	0.005	1,798
White	Israel Ashkenazi and Non Ashkenazi Jews	0.032	146
White	Iran Baloch	0.04	100

[1] Range of allele frequencies are reported based on the allele frequencies from Allele Frequencies.net (21). Those with a sample size of 100 or more were collected and populations were then grouped by OMB Racial/ethnic category group designations.

Supplemental Table S3. Evidence Linking Genotype with Phenotype

Type of Experimental Model (in vitro, in vivo preclinical, or clinical)	Major Findings	References	Level of Evidence
Clinical/case reports/*in vitro*	Patients with one or two copies of the *HLA-B*58:01* allele may have an increased risk of Severe Cutaneous Adverse Reactions, such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis, when treated with allopurinol as compared to patients with no *HLA-B*58:01:01* alleles or negative for the *HLA-B*58:01* test. Other genetic and clinical factors may also influence a patient's risk of allopurinol-induced adverse reactions.	Park, *et al.* (2015) (22) Zhang, *et al.* (2014) (23) Jung, *et al.* (2014) (24) Zhang, *et al.* (2014) (23) Chung, *et al*. (2014) (7) Tohkin, *et al*.(2013) (25) Yun, *et al*. (2013) (26) Goncalo, *et al.* (2013) (27), Niihara, *et al.* (2013) (28) Lee, *et al.* (2013) (29) Huang, *et al.* (2012) (30) Atzori, *et al.* (2012) (31) Cao, *et al.* (2012) (32) Chiu, *et al.* (2012) (33) Lee, *et al.* (2012) (34)	High

		Cristallo, *et al*.(2011) (35) Jung, *et al.* (2011) (36) Kang, *et al.* (2011) (37) Somkrua, *et al.* (2011)(38) Tassaneeyakul, *et al.* (2009)*(39)* Kemen, *et al.* (2009)(40) Kaniwa, *et al.* (2008) (41) Lonjou, *et al.* (2008)*(42)* Kano, *et al.* (2008) (43) Dainichi, *et al.* (2007)(44) Hung, *et al.* (2005)(11)	
Clinical	*HLA-B*58:01* is not associated with allopurinol-induced maculopapular eruptions or simple rash.	Jung, *et al.* (2014) (24) Goncalo, *et al.* (2013)(27) Jung, *et al.* (2011*)* (36) Lee, *et al.* (2012) (34)	Moderate
Clinical	Clinical trial conducted in Taiwan which genotyped for *HLA-B*58:01* before allopurinol use demonstrated that genotyping for this allele greatly reduces the incidence of allopurinol induced SCAR.	Kuo, et al. (2015)*	Moderate
Clinical/case reports	Patients with one or two copies of the *HLA-A*33:03*[a] allele who are treated with allopurinol may have an	Tohkin*, et al.* (2013) (25) Niihara, *et al.* (2013) (28)	Moderate

	increased risk of severe cutaneous adverse reactions (42) as compared to patients with no *HLA-A*33:03* alleles or negative for the *HLA-A*33:03* test. This allele has been shown to be in linkage disequilibrium with the *HLA-B*58:01* allele in some populations, which has a strong association with allopurinol-induced SCAR. Other genetic and clinical factors may also influence a patient's risk of allopurinol-induced adverse reactions.	Cristallo*, et al.* (2011) (35) Jung, *et al.* (2011) (36) Kang*, et al.* (2011) (37) Dainichi, *et al.* (2007) (44) Hung, *et al.* (2005) (11)	
Clinical	Patients with one or two copies of the *HLA-C*03:02*[b] allele who are treated with allopurinol may have an increased risk of severe cutaneous adverse reactions as compared to patients with no *HLA-C*03:02* alleles or negative for the *HLA-C*03:02* test. This allele has been shown to be in linkage disequilibrium with the *HLA-B*58:01* allele in some populations, which has a strong association with allopurinol-induced SCAR. Other genetic and clinical factors may also influence a patient's risk of allopurinol-induced adverse reactions.	Tohkin, *et al.* (2013)(25) Cristallo, *et al.* (2011)(35) Jung, *et al.* (2011)(36) Kang, *et al.* (2011)(37) Hung, *et al.* (2005)(11)	Moderate

[a]Some of the studies did not define the *HLA-A*33:03* allele, and reported *HLA-B*33* by low resolution DNA typing.

[b]Some of the studies did not define *HLA-C*03:02* and just reported the allele as *HLA-Cw3.*

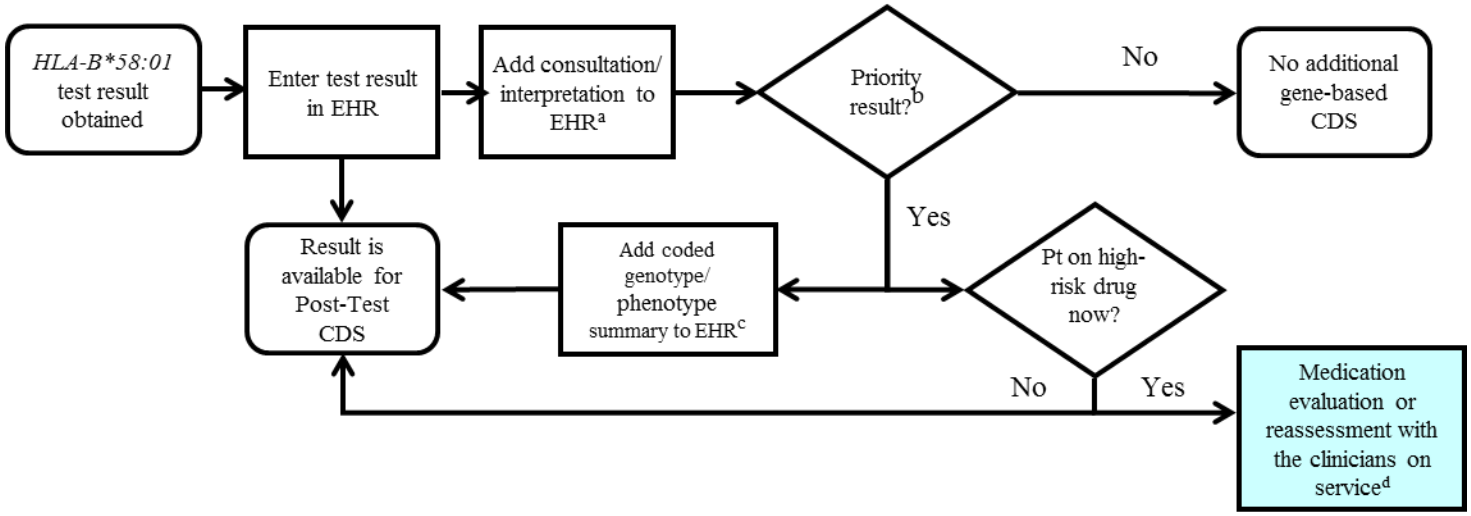
*Ko et al., *HLA-B*58:01* genotyping to prevent allopurinol induced severe cutaneous adverse reactions: national prospective study. Under review.

Supplemental Table S4. Drug(s) that pertain to this guideline.

Drug or Ingredient	**Source**	**Code Type**	**Code**
Allopurinol	RxNorm	RxCUI	519
Allopurinol	DrugBank	Accession Number	**DB00437**
Allopurinol	ATC	ATC Code	M04AA01
Allopurinol	PharmGKB	PharmGKB ID	PA448320
Febuxostat	RxNorm	RxCUI	73689
NA	DrugBank	Accession Number	NA
Febuxostat	ATC	ATC Code	M04AA03
Febuxostat	PharmGKB	PharmGKB ID	PA165958521

Supplemental Table S5.Gene(s) that pertain to this guideline

Gene Symbol	**Source**	**Code Type**	**Code**
HLA-B	HGNC	Symbol	HLA-B
HLA-B	HGNC	HGNC ID	4932
HLA-B	NCBI	Gene ID	3106
HLA-B	Ensembl	Ensembl ID	ENSG00000234745
HLA-B	PharmGKB	PharmGKB ID	PA35056



Blue shading indicates interaction with provider

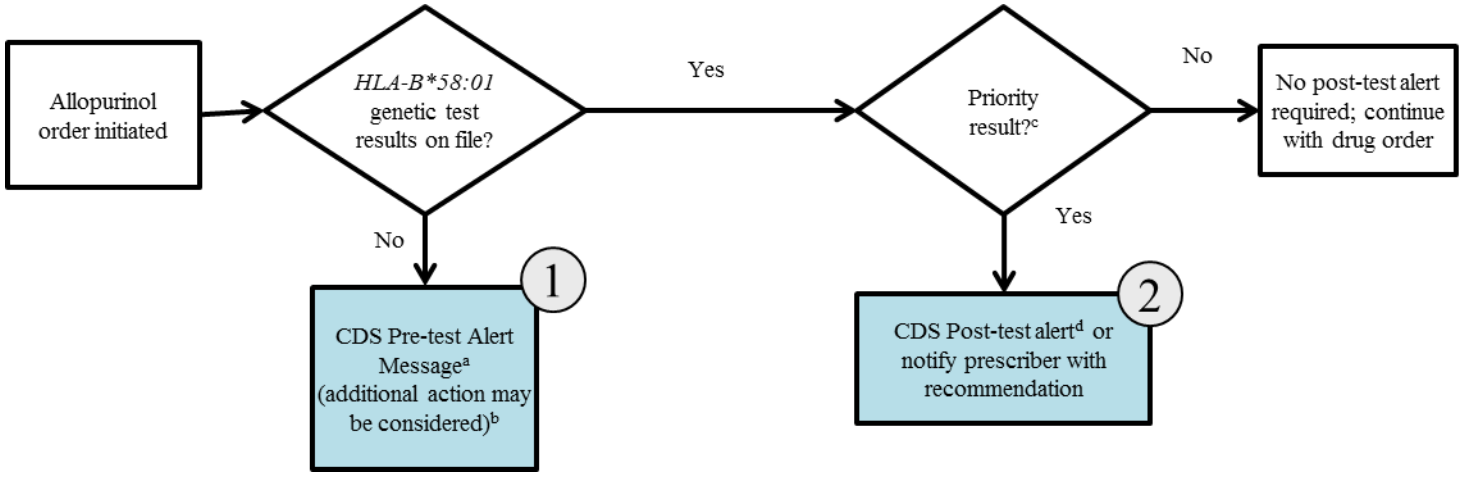
Supplemental Figure S1. *HLA-B*58:01* Pharmacogenetic Test Result: Clinical Implementation Workflow for EHR

[a]See **Supplementary Table S6** for diplotype/phenotype specific example

[b]"Priority result" is defined as a genetic test result that necessitates a change in drug, drug dose, or drug monitoring now or potentially in the future.

[c]Documentation in the EHR is institution specific. Optimally, the phenotype and/or genotype are available in the EHR to permanently inform prescribing decisions. See **Supplementary Table S7** for genotype/phenotype-specific summaries.

[d]Typically, SCAR develops within weeks or a few months of initiating treatment, but longer delays may occur. If a patient positive for *HLA-B*58:01* has been taking allopurinol for greater than three months, monitor closely for signs of hypersensitivity.



Note: Circled numerals refer to ***Supplementary Table S7***

Supplemental Figure S2.*HLA-B*58:01* Genotype and Allopurinol: Point of Care Clinical Decision Support

[a]See **Supplementary Table S7** for diplotype/phenotype specific pre-test alert example.
[b]Additional actions may include ordering a pharmacogenetic test, preventing the clinician from ordering the medication or allowing the clinician to cancel out of the alert.
[c]Priority result defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.
[d]See **Supplementary Table S7** for diplotype/phenotype specific post-test alert example.

Supplemental Table S6.Example Implementation of this Guideline: Pharmacogenetic Genotype/Phenotype Summary Entries

Test Result for *HLA-B*58:01*[b]	Coded Genotype/Phenotype Summary[c]	EHR Priority Result Notation[d]	Consultation (Interpretation) Text Provided with Test Result[e]
Negative	None	Normal/Low Risk[e]	The *HLA-B*58:01* allele, associated with allopurinol hypersensitivity, was not detected in this patient. Allopurinol can be used per standard dosing guidelines. Patients should be monitored closely for any signs of sensitivity reactions, especially those patients receiving allopurinol (of >300 mg/day), concomitant medications (i.e. thiazide diuretics or penicillin/cephalosporin) or with medical conditions (i.e. chronic kidney disease) that increase the non-genetic risk for allopurinol-related hypersensitivity reactions.
Positive	*HLA-B*58:01*Carrier	Abnormal/Priority /High Risk[e]	The *HLA-B*58:01* allele, associated with allopurinol hypersensitivity, was detected in this patient. Allopurinol is contraindicated.

[a]This table is provided to show examples of how a test result could be translated into discrete fields within an EHR, including a brief interpretation that summarized the result. The information presented here is consistent with the guideline but may need to be adapted to a given EHR's design and capabilities. Various EHRs or organizations may require different terms, and so different options are provided.
[b]Genetic tests for *HLA-B*58:01* are usually reported as positive (patient has the *HLA-B*58:01* allele) or negative (patient does not have the allele).
[c]The coded genotype/phenotype summary is used to store an interpretation of the test result. This is a design decision that may differ among sites.
[d]For this example, a priority result is defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.
[e]The specific wording of the interpretive text may differ among sites.

Supplemental Table S7. Example Implementation of this Guideline: Point of Care Clinical Decision Support

Flow Chart Reference Point[a]	CDS Context, Relative to Genetic Testing	Trigger Condition	CDS Alert Text[b]
1	Pre-Test	No *HLA-B*58:01* result on file	An *HLA-B*58:01* genotype test does not appear to have been ordered for this patient. Patients who carry this allele are at increased risk of serious dermatologic reactions with the use of allopurinol, including Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome. Please consult a clinical pharmacist[c] for more information.
2	Post-Test	*HLA-B*58:01*Carrier	The patient carries the *HLA-B*58:01* allele, which indicates that the patient is at risk of developing a serious dermatologic reaction, including Toxic Epidermal Necrolysis or Stevens-Johnson Syndrome. Allopurinol is contraindicated. Please consult a clinical pharmacist[c] for more information.

[a]See**Supplemental Figure S2**.

[b]The specific wording of the alert text may differ among sites.

[c]Pharmacist, pharmacologist, or a clinician with pharmacogenetic expertise/training.

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