WASHINGTON STATE UNIVERSITY

Pharmacogenomics of Drug-Induced Hypersensitivity Reactions

Rustin D. Crutchley, PharmD, AAHIVP

Scholarly Associate Professor

Program Director, Interprofessional Clinical Pharmacogenomics Certificate Program

Department of Pharmacotherapy

Conflict of Interest Disclosure

- Nothing to disclose

Learning Objectives

Describe background on the human leukocyte antigen (HLA) complex and its association with drug induced hypersensitivity reactions involving neurologic agents (phenytoin, carbamazepine and oxcarbazepine), allopurinol and abacavir

Determine the impact of genetic variation on drug pharmacokinetics, pharmacodynamics, and drug response

Interpret pharmacogenomic test results by identifying clinically actionable drug-gene pairs using high-quality, evidence-based pharmacogenomic databases and guidelines to formulate therapeutic recommendations

Recommend pharmacogenomic testing when appropriate and integrate test results with other clinical variables to optimize medication therapy

Discuss case examples utilizing various pharmacogenomic testing results to inform appropriate selection of neurologic agents (phenytoin, carbamazepine and oxcarbazepine), allopurinol and abacavir

Describe background on the human leukocyte antigen (HLA) complex and its association with drug induced hypersensitivity reactions involving neurologic agents (phenytoin, carbamazepine and oxcarbazepine), allopurinol and abacavir

Human Leukocyte Antigen (HLA)

- HLA helps the immune system distinguish self from non-self (foreign invaders like viruses or bacteria)
- HLA is the human version of the major histocompatibility complex (MHC)
  - More than 220 genes located on chromosome 6
  - Highly polymorphic
- Allows each person's immune system to react to a wide range of foreign invaders
- More than 100 diseases have been associated with different alleles of histocompatibility complex genes
- **Certain HLA types can predispose patients to drug induced hypersensitivity reactions**

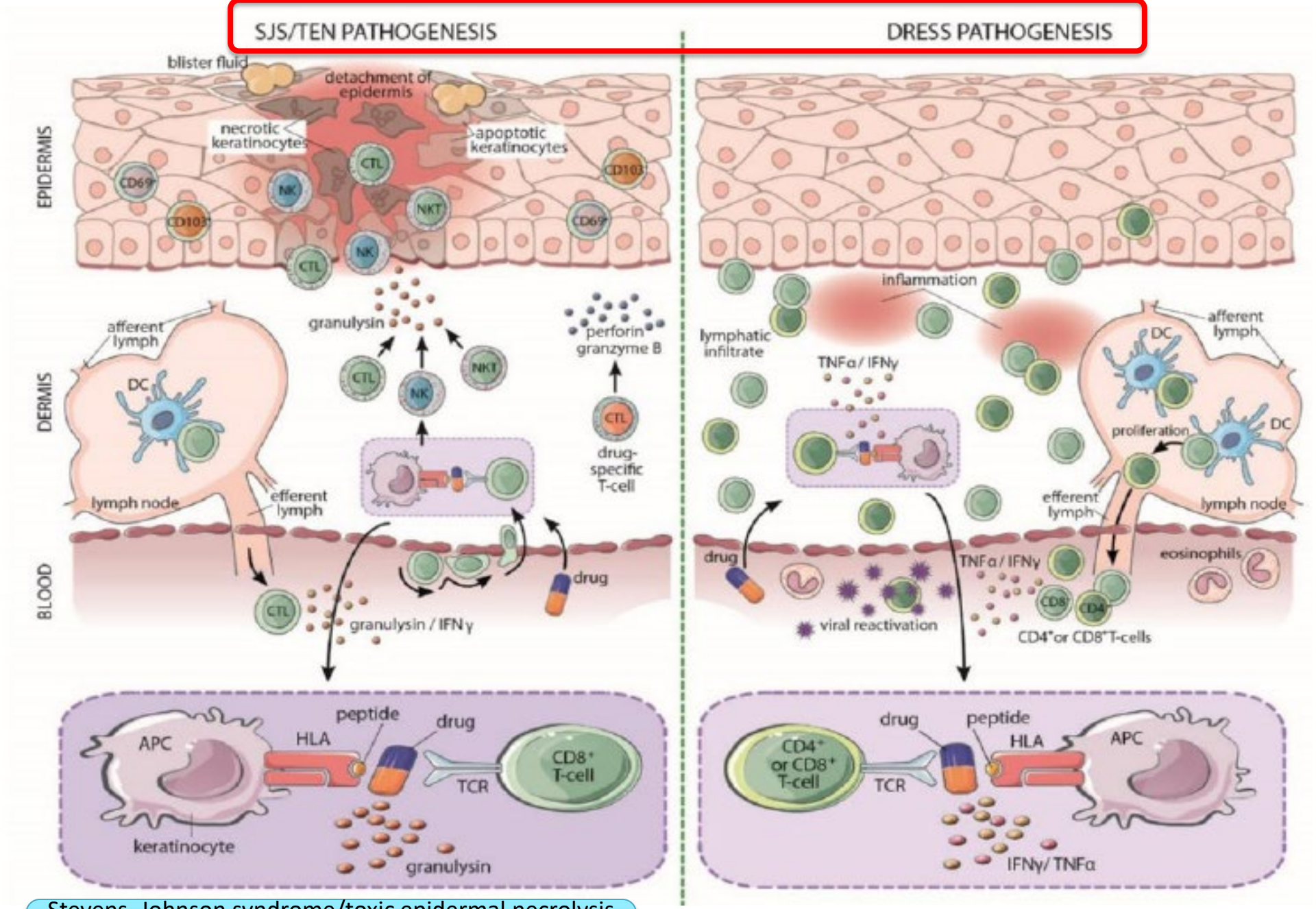
Human Leukocyte Antigen (HLA)

- *Genes in the HLA complex fall into 3 subgroups:*
  - **MHC Class I**
    - **HLA-A, HLA-B**, HLA-C
      - Present on all nucleated cells/recognized by CD8+ T cells
      - Display peptides to the immune system, if recognized as foreign it will trigger an immune response
      - Cellular immunity
  - **MHC Class II**
    - HLA-DP, HLA-DR, HLA-DQ
      - Found on antigen presenting cells (APCs)/recognized by CD4+ T cell
      - Specific immunity
  - **MHC Class III**
    - Involved in inflammation and other immune system activities

Serious Cutaneous Adverse Reaction (SCAR) - SJS/TEN

- Immune mediated reaction that affects skin and mucous membranes
  - Drug induced hypersensitivity reaction
- Rare and serious reaction that normally requires hospitalization
- Mortality rates are related to:
  - Age, drug half-life, and how early offending agent is discontinued
- **SJS** = Stevens-Johnson Syndrome
  - Epidermal detachment affecting up to 10% of the BSA
- **TEN** = Toxic Epidermal Necrolysis
  - Involves more than 30% of the BSA
- **SJS/TEN overlap syndrome**
  - Patients who have between 10-30% BSA blistered

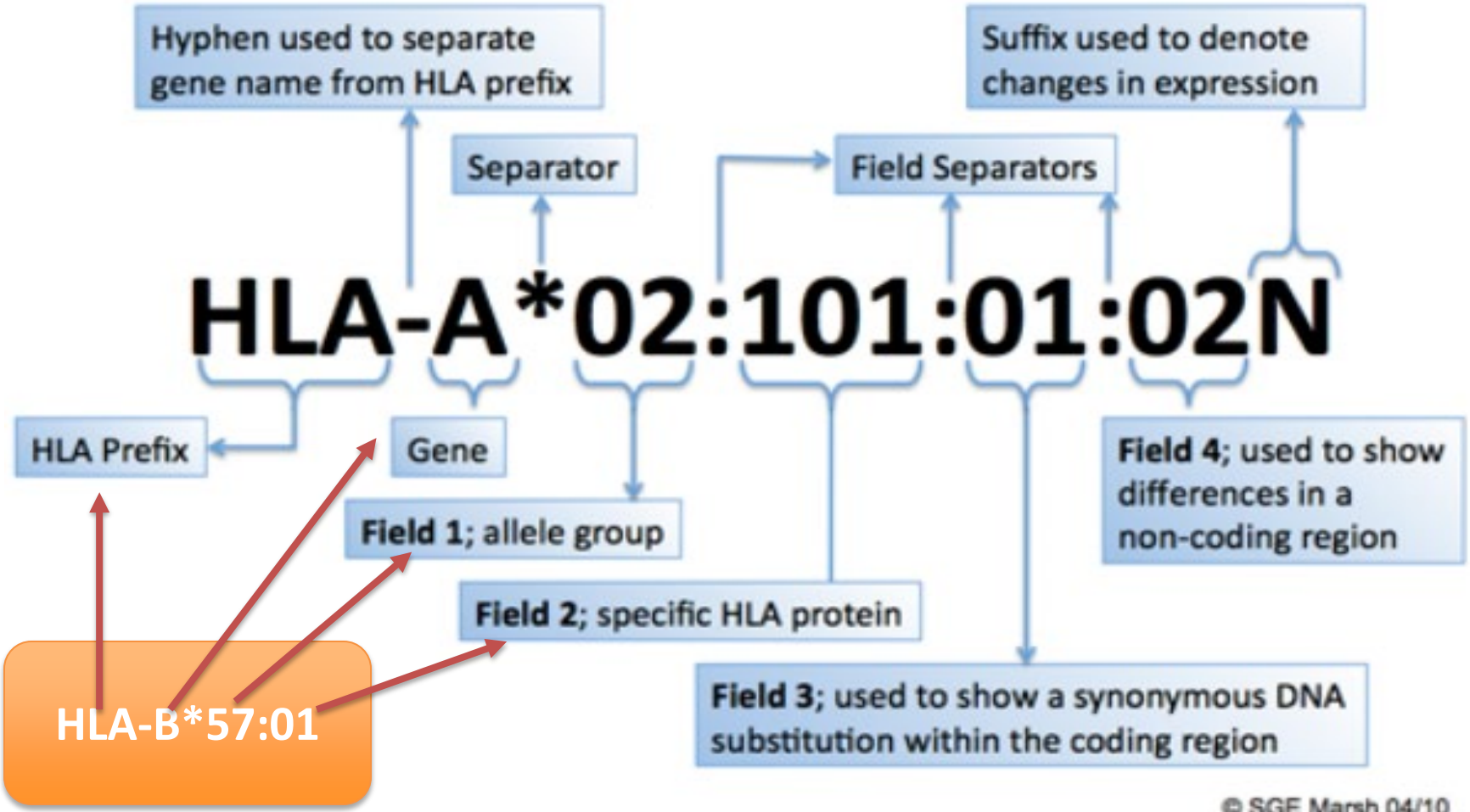
Phillips EJ et al. *Clin Pharmacol Ther*. 2018; 103(4): 574–581.



Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS)

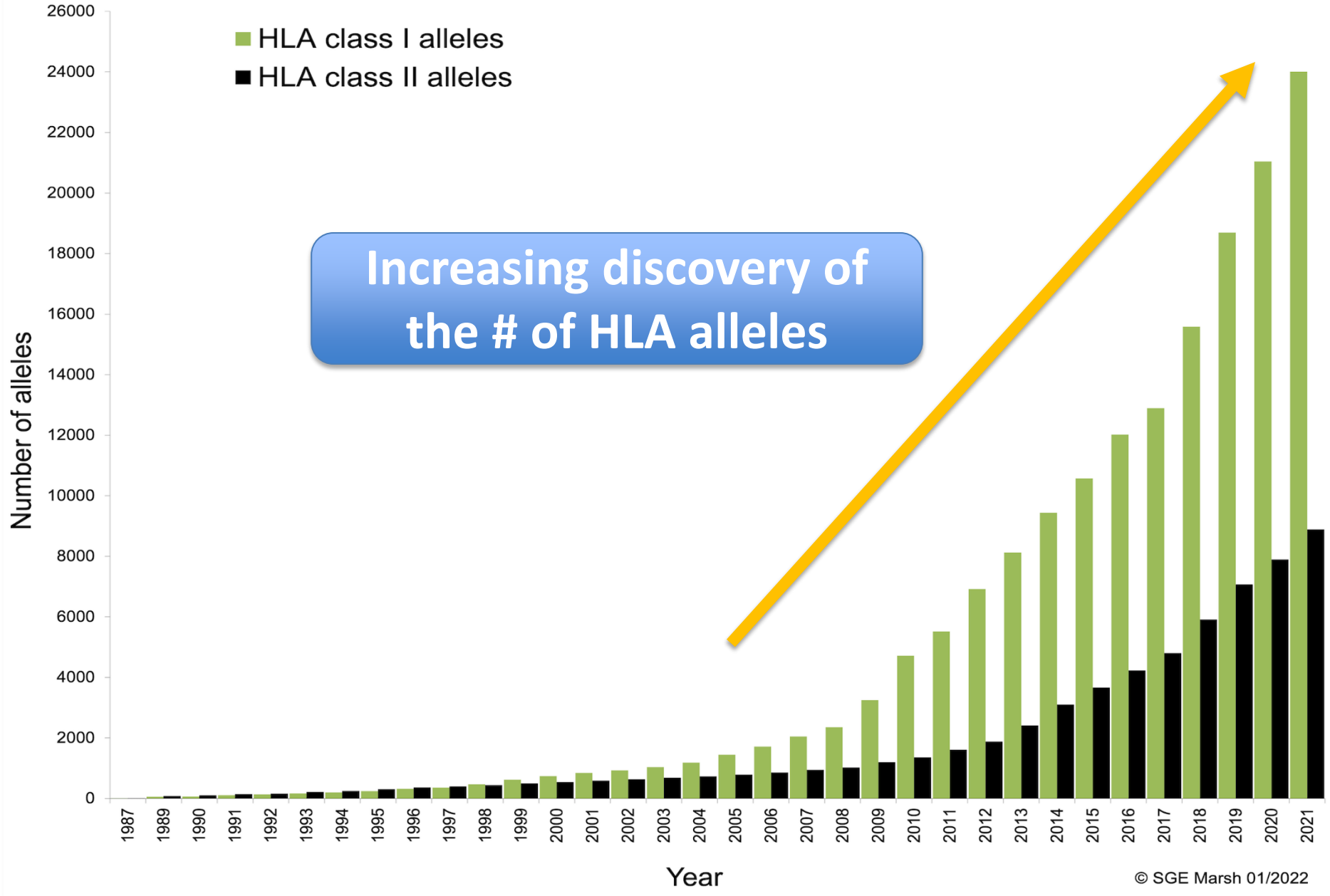
Karnes JH et al. *Annu Rev Pharmacol Toxicol*. 2019; 59:463–486.

HLA Nomenclature Classification



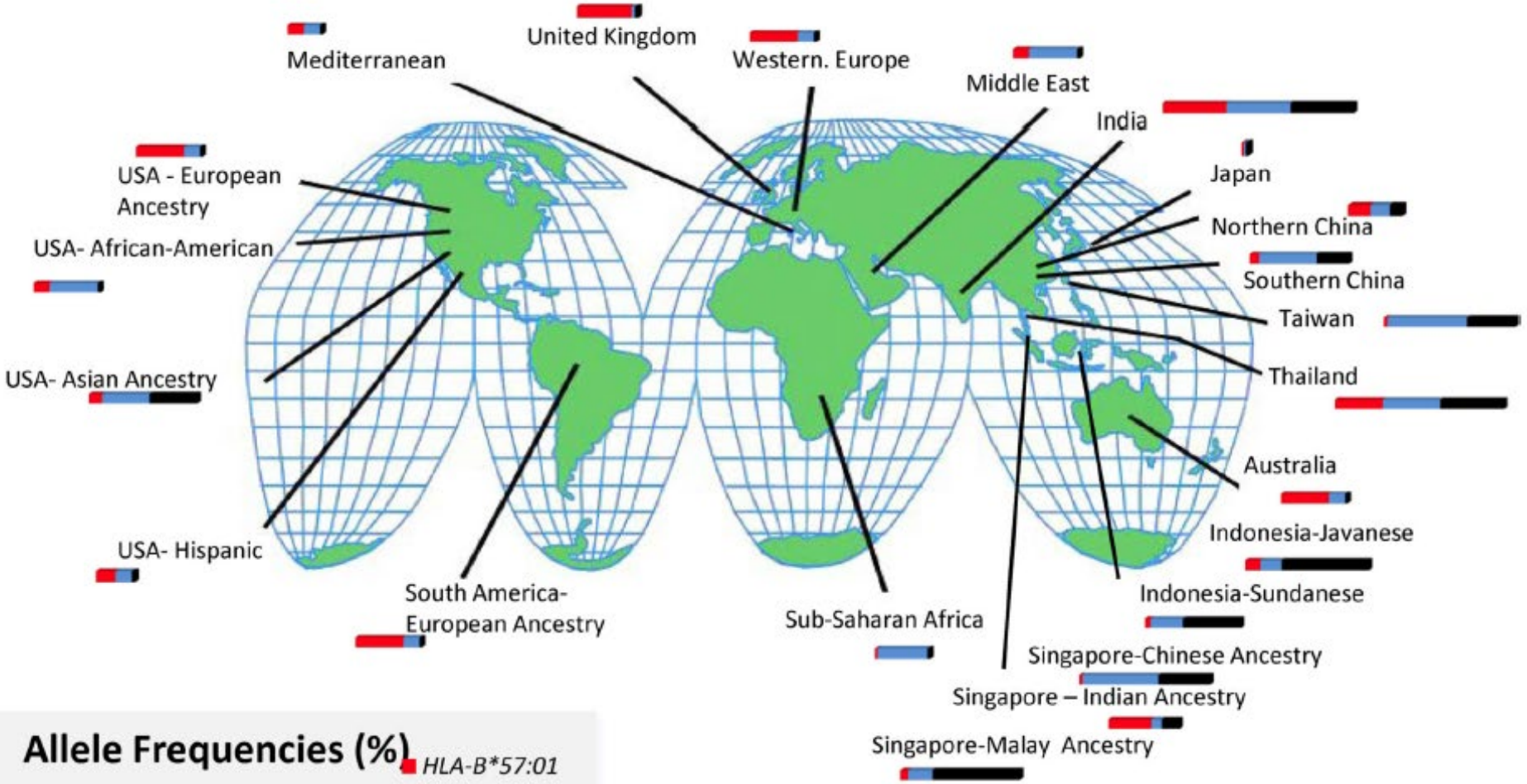
*first four-digits characterizes amino acid sequence variation

SGE Marsh et al: Nomenclature for factors of the HLA system, 2010. *Tissue Antigens* 2010 **75**:291-455
http://hla.alleles.org/nomenclature/naming.html Accessed March 29, 2022



SGE Marsh et al: Nomenclature for factors of the HLA system, 2010. *Tissue Antigens* 2010 **75**:291-455

Global Frequency of Drug-Specific HLA Alleles



Manolio TA et al. *Clin Pharmacol Ther*. 2018; 103(3): 390–394.

Determine the impact of genetic variation on drug pharmacokinetics, pharmacodynamics, and drug response

HLA-B*15:02 Genotype

- "*Positive*" = 1 or 2 copies of HLA-B*15:02 are present
- "*Negative*" = NO copies are present
- Allele frequencies of HLA-B*15:02
  - East Asian and Central/South Asian populations (1-20%)
  - European populations (0-1%)

- **HLA-B*15:02 can affect the following medications**
  - Phenytoin/fosphenytoin
  - Carbamazepine
  - Oxcarbazepine

Phillips EJ et al. *Clin Pharmacol Ther*. 2018; 103(4): 574–581.
Karnes JH et al. *Clin Pharmacol Ther*. 2021; 109(2): 302–309.

Phenytoin/ HLA-B*15:02 Genotype

- Fosphenytoin is the prodrug of phenytoin
- *MOA*: decreases influx of Na+ ions across cell membranes
- Commonly used for treatment of focal & generalized convulsive status epilepticus
  - Maintenance treatment **(therapeutic range of total phenytoin concentrations = 10-20 mg/L)**
- Highly unusual PK that require adjustments given demographic factors
  - Patient weight, sex and age
- Acute dose-related adverse drug reactions (ADRs)
  - Sedation, ataxia, dizziness, nystagmus, nausea, cognitive impairment
- **Metabolism of phenytoin is primarily by CYP2C9**
- HIGHLY allergenic
  - Rashes range from mild eruptions to life-threatening hypersensitivity reactions including **SJS/TEN (association with carriers of HLA-B*15:02)**

Karnes JH et al. *Clin Pharmacol Ther*. 2021; 109(2): 302–309.

Phenytoin PGx: HLA Factors

HLA Factor	Variant Allele	Allele Function	Examples of Medications	CPIC Level	PharmGKb Level of Evidence
HLA-B*15:02 (rs2395148)	Negative	Normal risk of SJS/TEN	Phenytoin Fosphenytoin	A	1A
	Positive	Increased risk of SJS/TEN			

Karnes JH et al. *Clin Pharmacol Ther*. 2021; 109(2): 302–309.

Phenytoin PGx: PK Factors

PK Factor	Variant Allele	Activity Score (AS)	Allele Function/ Phenotype	Examples of Medications	CPIC Level	PharmGKb Level of Evidence
CYP2C9	*1/*1	2	2 normal function alleles = **NORMAL (extensive) metabolizer**	Phenytoin Fosphenytoin	A	1A
	*1/*2 OR *1/*3 OR *2/*2	1.5 1 1	1 normal + 1 decreased 1 normal + 1 no function 2 decreased function = **INTERMEDIATE metabolizer**			
	*2/*3 OR *3/*3	0.5 0	1 no function + 1 decreased 2 no function = **POOR metabolizer**			

Karnes JH et al. *Clin Pharmacol Ther*. 2021; 109(2): 302–309.

Therapeutic Recs for Phenytoin

Table 3 Recommended dosing of phenytoin/fosphenytoin based on *HLA-B*15:02* and *CYP2C9* phenotype/genotype

*HLA-B*15:02* phenotype	CYP2C9 phenotype	Implication	Therapeutic recommendation	Classification of recommendation	Considerations
*HLA-B*15:02* positive	Any CYP2C9 phenotype	Increased risk of phenytoin-induced SJS/TEN	If patient is phenytoin-naïve, do not use phenytoin/fosphenytoin. Avoid carbamazepine and oxcarbazepine.	Strong	Other aromatic anticonvulsants, including eslicarbazepine, lamotrigine, and phenobarbital, have weaker evidence linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used in choosing an alternative agent.
			If the patient has previously used phenytoin continuously for longer than 3 months without incidence of cutaneous adverse reactions, cautiously consider use of phenytoin in the future. The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (4–28 days), and cases usually occur within 3 months of dosing.	Optional	Previous tolerance of phenytoin is not indicative of tolerance to other aromatic anticonvulsants.

Karnes JH et al. *Clin Pharmacol Ther*. 2021; 109(2): 302–309.

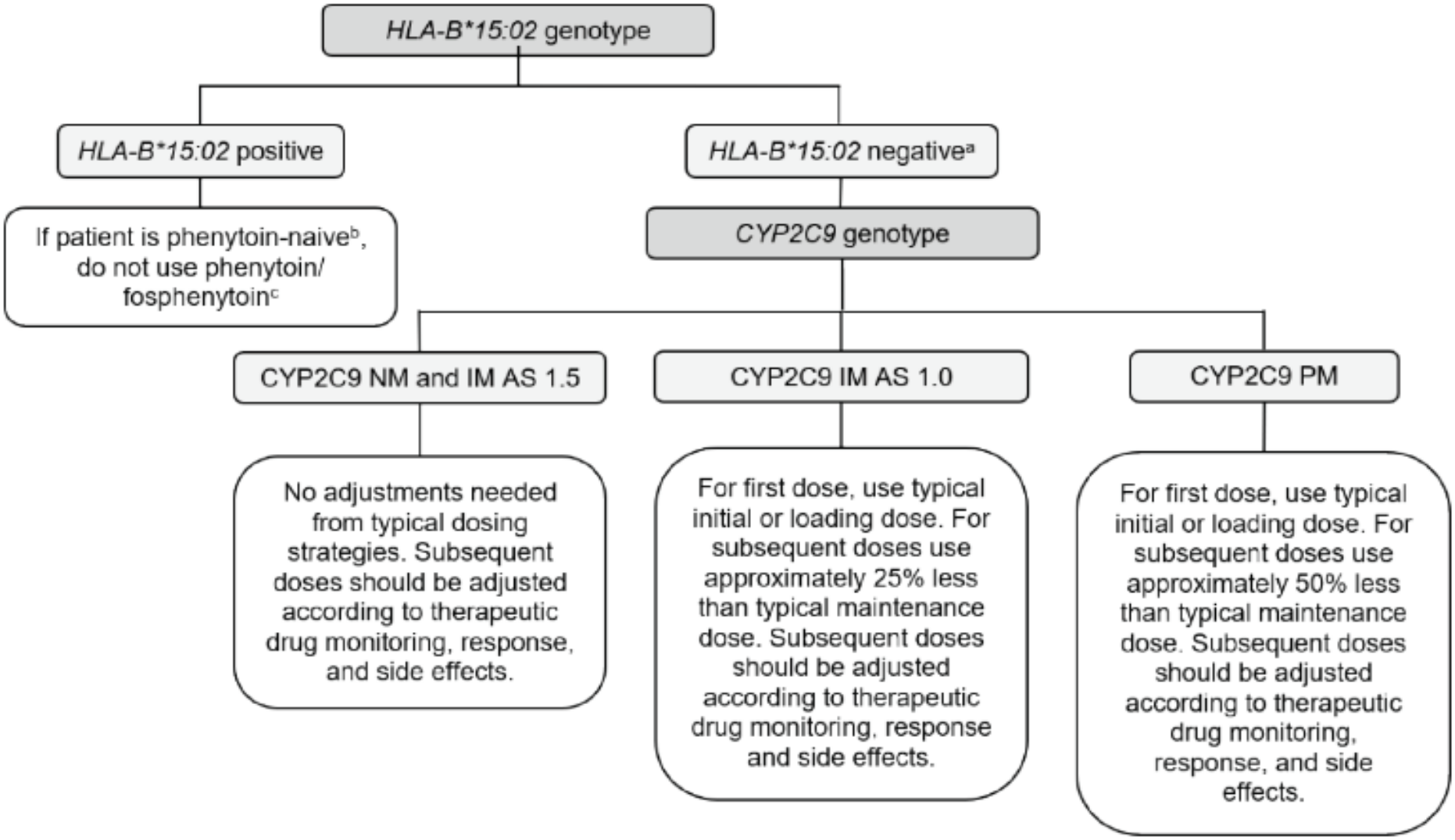
Therapeutic Recs for Phenytoin

*HLA-B*15:02* negative	CYP2C9 NM	Normal phenytoin metabolism	No adjustments needed from typical dosing strategies. Subsequent doses should be adjusted according to therapeutic drug monitoring, response, and side effects. An *HLA-B*15:02* negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Strong
*HLA-B*15:02* negative	CYP2C9 IM AS 1.5	Slightly reduced phenytoin metabolism; however, this does not appear to translate into increased side effects	No adjustments needed from typical dosing strategies. Subsequent doses should be adjusted according to therapeutic drug monitoring, response and side effects. An *HLA-B*15:02* negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice	Moderate
*HLA-B*15:02* negative	CYP2C9 IM AS 1.0	Reduced phenytoin metabolism; higher plasma concentrations will increase probability of toxicities.	For first dose, use typical initial or loading dose. For subsequent doses, use ~ 25% less than typical maintenance dose. Subsequent doses should be adjusted according to therapeutic drug monitoring, response and side effects. An *HLA-B*15:02* negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Moderate
*HLA-B*15:02* negative	CYP2C9 PM	Reduced phenytoin metabolism; higher plasma concentrations will increase probability of toxicities.	For first dose, use typical initial or loading dose. For subsequent doses use ~ 50% less than typical maintenance dose. Subsequent doses should be adjusted according to therapeutic drug monitoring, response, and side effects. An *HLA-B*15:02* negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Strong
*HLA-B*15:02* negative	Indeterminate	n/a	n/a	No recommendation

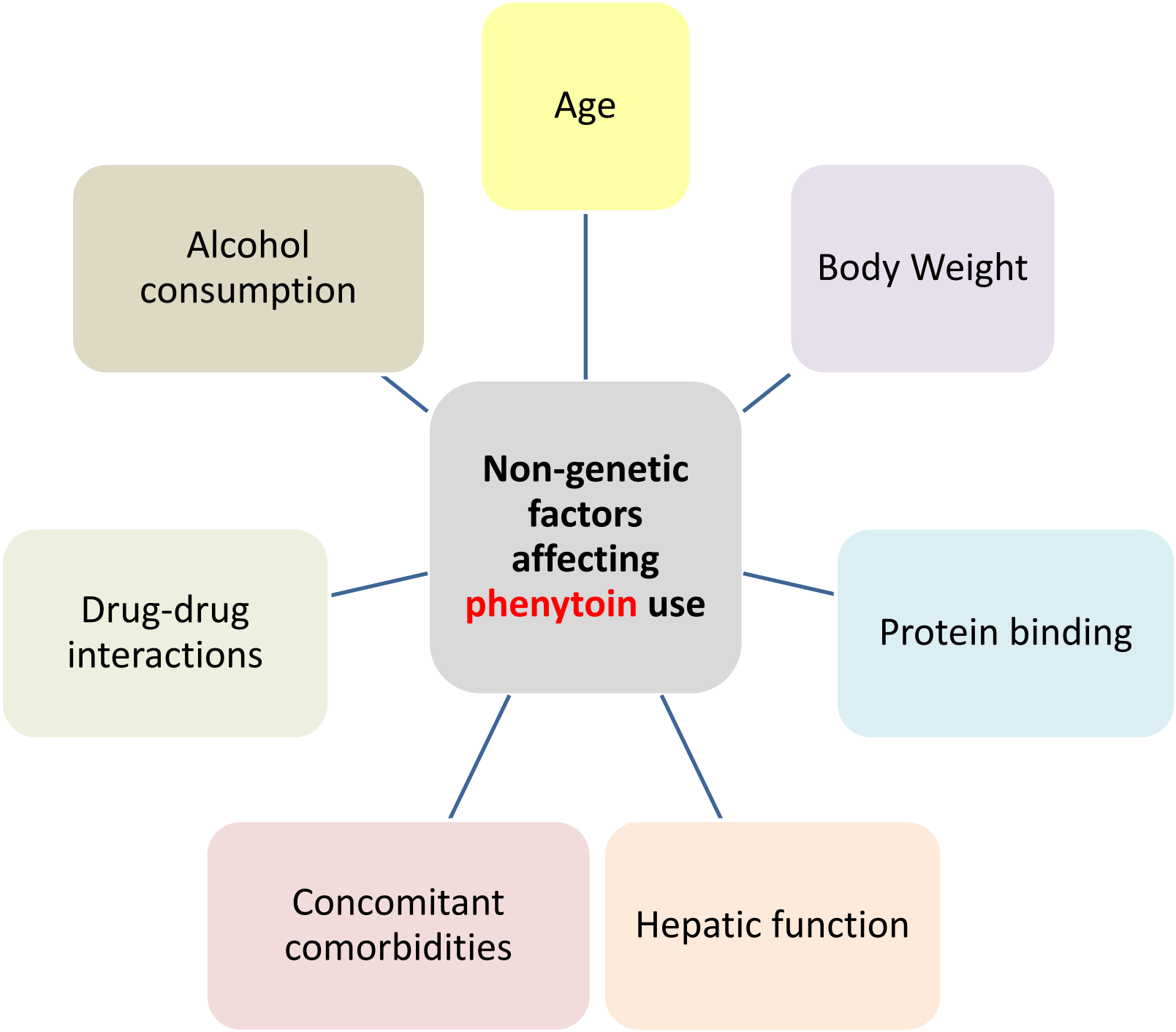
AS, activity score; IM, intermediate metabolizer; n/a, not applicable; NM, normal metabolizer; PM, poor metabolizer; SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

Karnes JH et al. *Clin Pharmacol Ther*. 2021; 109(2): 302–309.

PGx Guided Algorithm for Phenytoin



Karnes JH et al. *Clin Pharmacol Ther*. 2021; 109(2): 302–309.


Age
Alcohol consumption
Body Weight
Non-genetic factors affecting phenytoin use
Drug-drug interactions
Protein binding
Concomitant comorbidities
Hepatic function

HLA-A*31:01 Genotype

- Associated with wider range of **carbamazepine** hypersensitivity reactions
  - Maculopapular exanthema (MPE), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), and SJS/TEN
    - **DRESS** = severe hypersensitivity reaction
      - Cutaneous eruptions & life-threatening systemic manifestations
    - **MPE** = more mild reaction without systemic or organ involvement
  - Allele frequency of carriers of HLA-A*31:01
    - Caucasians (3%)
    - Hispanic/South Americans (6%)
    - East Asians (8% in Japanese and 5% in South Koreans)
    - South/Central Asians (2%)
  - Southeast Asian populations have a stronger association with HLA-B*15:02 versus HLA-A*31:01 hypersensitivity reactions

Phillips EJ et al. *Clin Pharmacol Ther*. 2018; 103(4): 574–581.

Carbamazepine/ HLA-A*31:01 Genotype

- **Carbamazepine** = an aromatic anticonvulsant, structurally related to the TCAs
- *MOA*: produces a frequency- and voltage-dependent block of Na+ channels
  - Reduces the propagation of repetitive action potentials in the brain
- **Indications**:
  - Bipolar disorder
  - Focal & generalized onset seizures
  - Trigeminal neuralgia
- Dose-dependent ADRs:
  - Dizziness, ataxia, nystagmus
- Other ADRs (complex dose-response):
  - Aplastic anemia, agranulocytosis, hyponatremia, liver injury
  - *Hypersensitivity reactions (SJS/TEN) can occur in carriers of:*
    - **HLA-A*31:01**
    - **HLA-B*15:02**

Phillips EJ et al. *Clin Pharmacol Ther*. 2018; 103(4): 574–581.

Carbamazepine PGx: HLA Factors

HLA Factor	Variant Allele	Allele Function	Examples of Medications	CPIC Level	PharmGKb Level of Evidence
HLA-A*31:01 (rs1061235)	Negative	Normal risk of SJS/TEN	Carbamazepine	A	1A
	Positive	Greater risk of SJS/TEN			
HLA-B*15:02 (rs2395148)	Negative	Normal risk of SJS/TEN	Carbamazepine	A	1A
	Positive	Greater risk of SJS/TEN			

Phillips EJ et al. *Clin Pharmacol Ther*. 2018; 103(4): 574–581.

Therapeutic Recs for Carbamazepine

Genotype[a]	Implication	Therapeutic recommendation	Classification of recommendation	Considerations for other aromatic anticonvulsants
*HLA-B*15:02* negative and *HLA-A*31:01* negative	Normal risk of carbamazepine-induced SJS/TEN, DRESS, and MPE	Use carbamazepine per standard dosing guidelines.[b]	Strong	N/A
*HLA-B*15:02* negative and *HLA-A*31:01* positive	Greater risk of carbamazepine-induced SJS/TEN, DRESS, and MPE	If patient is carbamazepine-naïve and alternative agents are available, do not use carbamazepine.	Strong	Other aromatic anticonvulsants[d] have very limited evidence, if any, linking SJS/TEN, DRESS, and/or MPE with the *HLA-A*31:01* allele, and thus no recommendation can be made with respect to choosing another aromatic anticonvulsant as an alternative agent.
		If patient is carbamazepine-naïve and alternative agents are not available, consider the use of carbamazepine with increased frequency of clinical monitoring. Discontinue therapy at first evidence of a cutaneous adverse reaction.	Optional	N/A
		The latency period for cutaneous adverse drug reactions is variable depending on phenotype; however, all usually occur within three months of regular dosing. Therefore, if the patient has previously used carbamazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine.	Optional	Previous tolerance of carbamazepine is not indicative of tolerance to other aromatic anticonvulsants.[d]

Phillips EJ et al. *Clin Pharmacol Ther*. 2018; 103(4): 574–581.

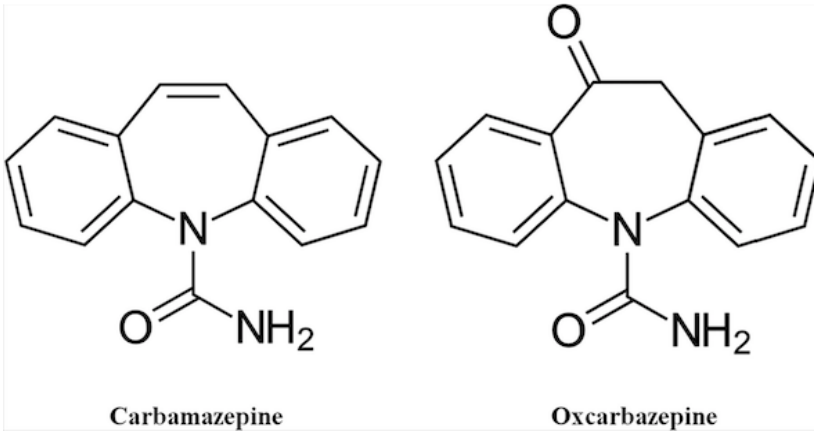
Therapeutic Recs for Carbamazepine

*HLA-B*15:02* positive[c] and any *HLA-A*31:01* genotype (or *HLA-A*31:01* genotype unknown)	Greater risk of carbamazepine-induced SJS/TEN	If patient is carbamazepine-naïve, do not use carbamazepine.	Strong	Other aromatic anticonvulsants[d] have weaker evidence linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used in choosing an alternative agent.
		The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (~4–28 days), and cases usually occur within three months of dosing; therefore, if the patient has previously used carbamazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine in the future.	Optional	Previous tolerance of carbamazepine is not indicative of tolerance to other aromatic anticonvulsants.[d]

Phillips EJ et al. *Clin Pharmacol Ther*. 2018; 103(4): 574–581.

Oxcarbazepine/ HLA-B*15:02 Genotype

- Keto-analog of carbamazepine
  - Similar indications and ADRs to carbamazepine
- Known hypersensitivity reaction to carbamazepine may result in predisposition to a similar reaction with **oxcarbazepine**
  - **HLA-B*15:02 ONLY**
  - Hypersensitivity reaction usually develops within **first 4-28 days** of therapy



Phillips EJ et al. *Clin Pharmacol Ther*. 2018; 103(4): 574–581.
Kim H et al. *Pediatrics*. 2018;141(s5):e20171361

Oxcarbazepine PGx: HLA Factors

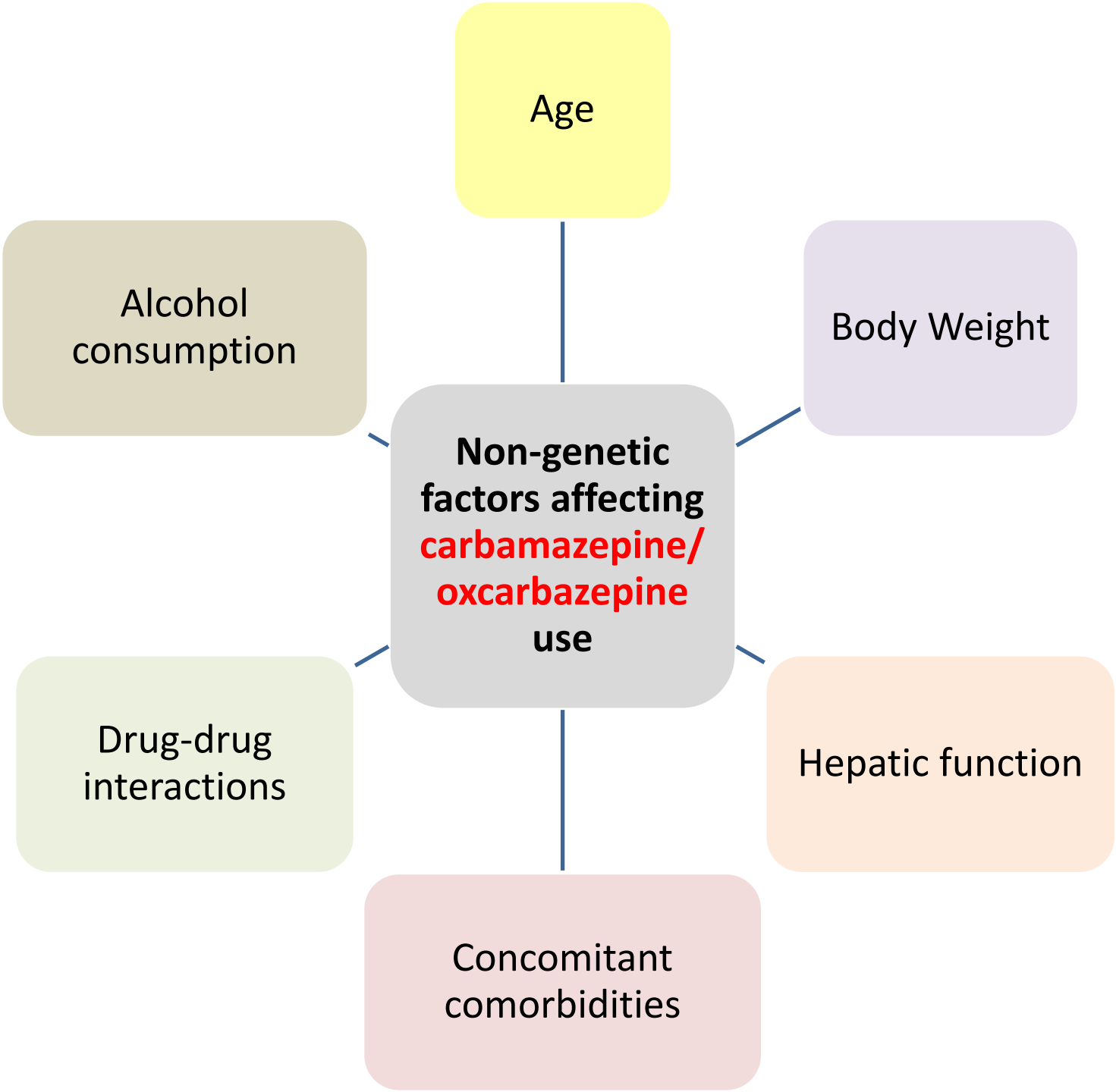
HLA Factor	Variant Allele	Allele Function	Examples of Medications	CPIC Level	PharmGKb Level of Evidence
HLA-B*15:02 (rs2395148)	Negative Positive	Normal risk of SJS/TEN Greater risk of SJS/TEN	Oxcarbazepine	A	1A

Phillips EJ et al. *Clin Pharmacol Ther*. 2018; 103(4): 574–581.

Therapeutic Recs for Oxcarbazepine

Genotype	Implication	Therapeutic recommendation	Classification of recommendation	Considerations for other aromatic anticonvulsants
*HLA-B*15:02* negative	Normal risk of oxcarbazepine-induced SJS/TEN	Use oxcarbazepine per standard dosing guidelines.	Strong	N/A
*HLA-B*15:02* positive	Greater risk of oxcarbazepine-induced SJS/TEN	If patient is oxcarbazepine-naïve, do not use oxcarbazepine.	Strong	Other aromatic anticonvulsants[a] have weaker evidence linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used in choosing an alternative agent.
		The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (~4–28 days), and cases usually occur within three months of dosing; therefore, if the patient has previously used oxcarbazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of oxcarbazepine in the future.	Optional	Previous tolerance of oxcarbazepine is not indicative of tolerance to other aromatic anticonvulsants.[a]

Phillips EJ et al. *Clin Pharmacol Ther*. 2018; 103(4): 574–581.


Age
Alcohol consumption
Body Weight
Non-genetic factors affecting carbamazepine/ oxcarbazepine use
Drug-drug interactions
Hepatic function
Concomitant comorbidities

PGx Testing Recommendations-Neurologic Agents

Drug	PharmGKB's interpretation of level of action implied in FDA label	FDA Table of PGx Associations
Carbamazepine		
HLA-A*31:01	Actionable	Results in higher adverse reaction risk (severe skin reactions). Consider risk and benefit of carbamazepine use in patients positive for HLA-A*31:01. Genotyping is not a substitute for clinical vigilance.
HLA-B*15:02	Testing required	Results in higher adverse reaction risk (severe skin reactions). Avoid use unless potential benefits outweigh risks and consider risks of alternative therapies. Patients positive for HLA-B*15:02 may be at increased risk of severe skin reactions with other drugs that are associated with a risk of Stevens Johnson Syndrome/Toxic Epidermal necrolysis (SJS/TEN). Genotyping is not a substitute for clinical vigilance
Oxcarbazepine		
HLA-B*15:02	Testing recommended	Results in higher adverse reaction risk (severe skin reactions). Patients positive for HLA-B*15:02 may be at increased risk of severe skin reactions with other drugs that are associated with a risk of Stevens Johnson Syndrome/Toxic Epidermal necrolysis (SJS/TEN). Genotyping is not a substitute for clinical vigilance

https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations Accessed March 30, 2022.
https://www.pharmgkb.org/labelAnnotation/PA166151882 Accessed March 30, 2022

PGx Testing Recommendations-Neurologic Agents

Drug	PharmGKB's interpretation of the level of action implied in FDA label	FDA Table of PGx Associations
Phenytoin		
HLA-B*15:02	Actionable	May result in higher adverse reaction risk (severe cutaneous reactions). Patients positive for HLA-B*15:02 may be at increased risk of Stevens Johnson Syndrome/Toxic Epidermal necrolysis (SJS/TEN). Consider avoiding phenytoin as an alternative to carbamazepine in patients who are positive for HLA-B*15:02. Genotyping is not a substitute for clinical vigilance and patient management.
CYP2C9	Actionable	**IM or PMs**: May result in higher systemic concentrations and higher adverse reaction risk (central nervous system toxicity). Refer to FDA labeling for specific dosing recommendations. **Carriers of CYP2C9*3 alleles** may be at increased risk of severe cutaneous adverse reactions. Consider avoiding phenytoin as an alternative to carbamazepine in patients who are CYP2C9*3 carriers. Genotyping is not a substitute for clinical vigilance and patient management.

https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations Accessed March 30, 2022

https://www.pharmgkb.org/labelAnnotation/PA166104860 Accessed March 30, 2022

Patient Case Example

- **CC:** AC is a 28-year-old Caucasian male who reports to the clinic with increased complaints of sedation, loss of coordination, dizziness and feeling rather nauseous. He also complains of uncontrolled repetitive movements of his eyes (also known as nystagmus). AC has a history of epilepsy for the past 10 years which was controlled with valproic acid. He started phenytoin 2 weeks ago after having a life-threatening episode of status epilepticus. AC notes that since then his seizures have been under control. His provider added phenytoin to AC's regimen 2 weeks ago ago since he has had prior success using this combination of valproic acid and phenytoin in some patients.
- **PMH:** Diagnosed with major depressive disorder and epilepsy after car accident 10 years ago. Most recently status epilepticus episode 2 weeks ago.
- **SH:** Drinks alcohol occasionally, denies smoking & recreational drug use.
- **Medications:** valproic acid 500 mg po twice daily, phenytoin 600 mg po once daily, and sertraline 100 mg po once daily
- **Vitals:** 84 kg, BP 95/62, HR 58, RR 14
- **Current labs:** total phenytoin = 32 mg/L, SCr 1.0 mg/dL, all other labs are WNL
- **PGx test results** (available on next slide)

Manchester University

FOR ACADEMIC PURPOSES ONLY - NOT FOR CLINICAL USE

REPORT NUMBER-10866	SPECIMEN DETAILS	ORDERED BY

SPECIMEN TYPE: Buccal Swab

AC's PGx Testing Results

Test Details

Gene	Genotype	Phenotype	Alleles Tested
CYP2C19	*1/*1	Normal Metabolizer	*2, *3, *4, *4B, *5, *6, *7, *8, *9, *17
CYP2D6	*1/*1	Normal Metabolizer	*2, *3, *4, *4M, *6, *7, *8, *9, *10, *12, *14A, *14B, *17, *29, *35, *41
CYP3A5	*3/*3	Poor Metabolizer	*1D, *2, *3, *3B, *3C, *6, *7, *8, *9
CYP3A4	*1/*1	Normal Metabolizer	*1B, *2, *3, *12, *17, *22
VKORC1	-1639G>A G/G	Low Warfarin Sensitivity	-1639G>A
CYP4F2	*1/*1	Normal Function	*2, *3
CYP2C9	*3/*4	Poor Metabolizer	*2, *3, *4, *5, *6, *11
CYP2B6	*1/*1	Normal Metabolizer	*6, *9
CYP1A2	*1F/*1F	Normal Metabolizer - Higher Inducibility	*1C, *1D, *1F, *1K, *1L, *1V, *1W
SLCO1B1	521T>C T/T	Normal Function	521T>C, 388A>G
CFTR	G551D/R553X	Positive	Numerous
DPYD	*2A/c.2846A>T	Poor Metabolizer	Numerous
TPMT NUDT15	*1/*2 *1/*1	Intermediate Metabolizer Normal Metabolizer	*2, *3A, *3B, *3C, *4 *2, *3, *4, *5, *6, *7, *8, *9
UGT1A1	*1/*1	Normal Metabolizer	*6, *27, *28, *36, *37, *60, *80
G6PD	A- or A–/Orissa	Deficient	Numerous

Additional Test Results (added to this original report)

HLA-B*15:02	negative/negative	Negative	HLA-A*31:01	negative/negative	Negative
HLA-B*57:01	negative/positive	Positive			
HLA-B*58:01	negative/negative	Negative			

Patient Case Example

Which of the following treatment strategies represents the best next step for managing AC's chief complaints?

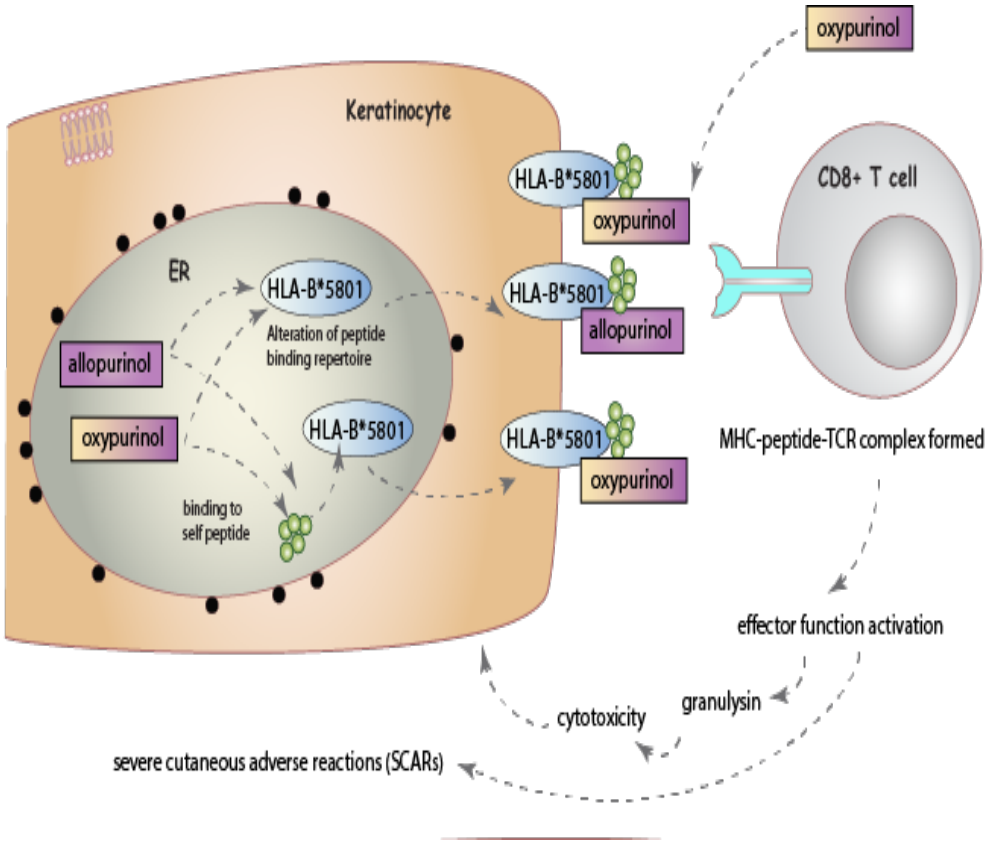
a. Reduce phenytoin dose to 450 mg daily
b. Reduce phenytoin dose to 300 mg daily
c. Continue same phenytoin dose of 600 mg daily since side effects will become more tolerable with time
d. Continue same phenytoin dose of 600 mg daily and increase valproic acid dosing to 750 mg twice daily

Benefits of PGx testing when considering neurologic agents (phenytoin, carbamazepine and oxcarbazepine)

- Determination of appropriate maintenance dose for phenytoin given CYP2C9 phenotype
  - Reduce the risk for toxicities associated with phenytoin
  - Improve therapeutic efficacy of a narrow therapeutic index (NTI) drug
- Avoid initiating therapy in patients who are carriers of HLA genotypes that may increase their risk for life-threatening hypersensitivity reactions
  - Avoid severe cutaneous adverse reactions (SCAR) such as SJS/TEN
  - PGx testing information can help guide earlier implementation of appropriate treatment
  - Reduce utilization of healthcare resources (i.e. avoiding SCAR requiring hospitalization and patient support/treatment)
- Still important to use **therapeutic drug monitoring (TDM)** with these agents (i.e. monitoring therapeutic drug concentrations)

Phillips EJ et al. *Clin Pharmacol Ther*. 2018; 103(4): 574–581.
Karnes JH et al. *Clin Pharmacol Ther*. 2021; 109(2): 302–309.

Allopurinol/HLA-B*58:01



- **Allopurinol** has a labeled indication for treatment of gout
- **MOA:** An analogue of purine-based hypoxanthine which inhibits the conversion of hypoxanthine and xanthine to uric acid via xanthine oxidase
- **Carrier of HLA-B*58:01 allele**
  - *Increases risk of severe cutaneous adverse reactions* during allopurinol administration
    - SJS/TEN
- Prevalence of HLA-B*58:01 carriers vary by race/ethnicity
  - 5.3% among Asians
  - 3.85% among African Americans/ Blacks
  - 1.45% among Native Hawaiian or Other Pacific Islanders
  - 1.35% among Hispanic or Latinos
  - 0.8% among Whites

Hershfield MS et al. *Clin Pharmacol Ther*. 2013;93(2):153-8
https://www.pharmgkb.org/pathway/PA165980774 Accessed March 30, 2022

Allopurinol PGx: HLA Factors

HLA Factor	Variant Allele	Allele Function	Examples of Medications	CPIC Level	PharmGKb Level of Evidence
HLA-B*58:01	Carrier Non-carrier	Increased risk of severe cutaneous adverse reactions Low or reduced risk of severe cutaneous adverse reactions	Allopurinol	A	1A

Hershfield MS et al. *Clin Pharmacol Ther*. 2013;93(2):153-8

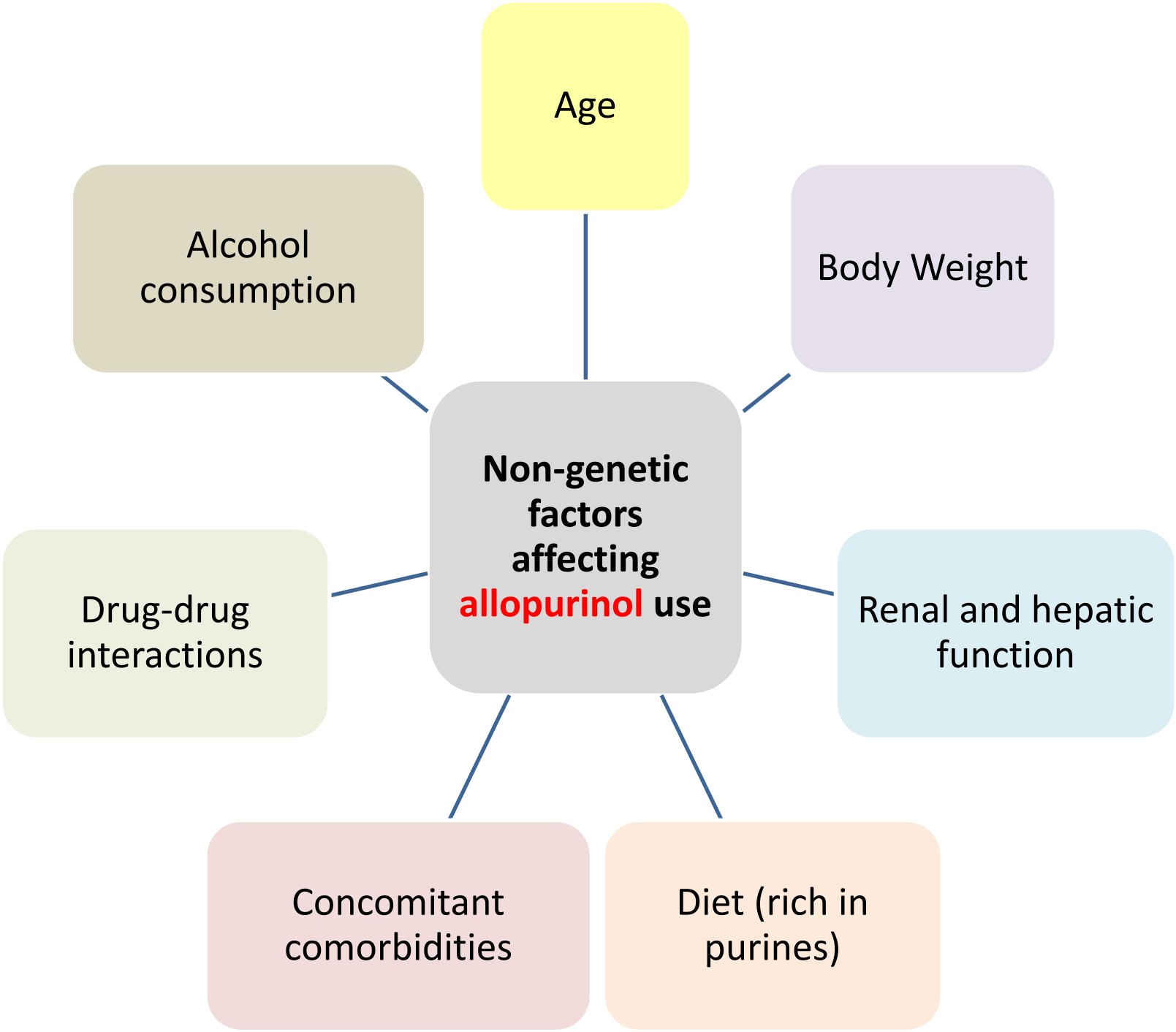
Therapeutic Recommendations for Allopurinol Use

Table 2 Recommended therapeutic use of allopurinol by *HLA-B* genotype

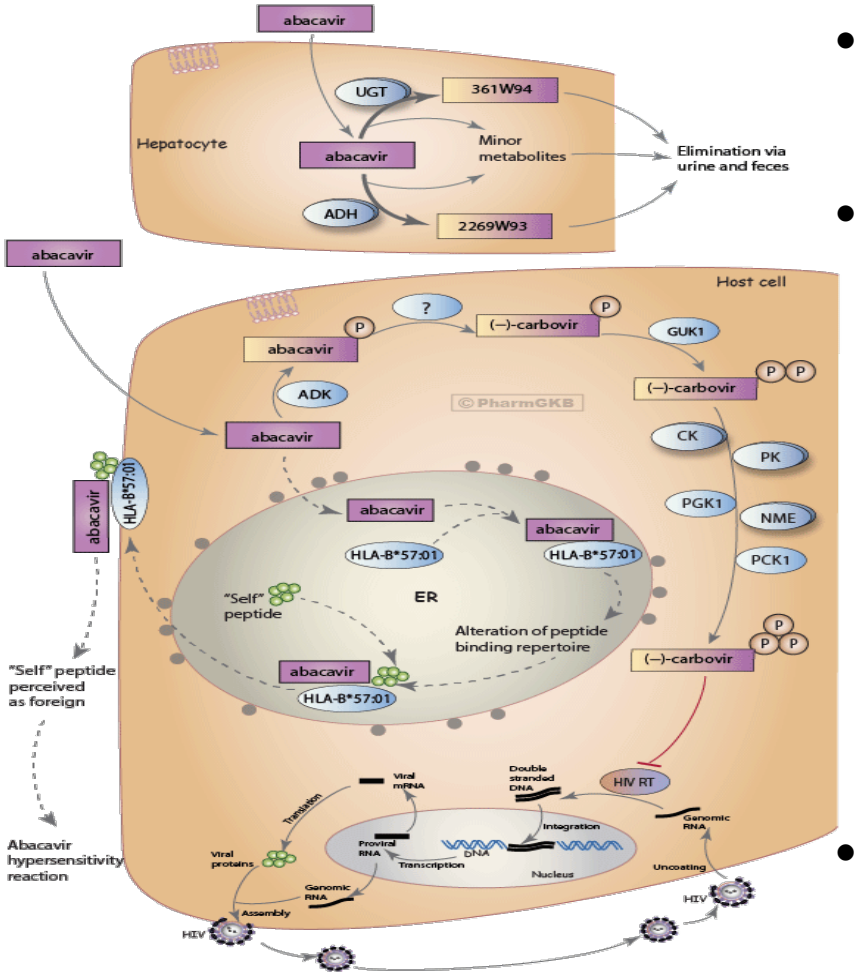
Genotype	Implications for phenotypic measures	Recommendations for allopurinol	Classification of recommendations[a]
Noncarrier of *HLA-B*5801* (*X/*X)[b]	Low or reduced risk of allopurinol-induced SCAR	Use allopurinol per standard dosing guidelines	Strong
Carrier of *HLA-B*5801* (*HLA-B*5801*/*X,[b] *HLA-B*5801*/*HLA-B*5801*)	Significantly increased risk of allopurinol-induced SCAR	Allopurinol is contraindicated	Strong

HLA-B, human leukocyte antigen-B; SCAR, severe cutaneous adverse reaction.

Hershfield MS et al. *Clin Pharmacol Ther*. 2013;93(2):153-8


Age
Alcohol consumption
Body Weight
Non-genetic factors affecting allopurinol use
Drug-drug interactions
Renal and hepatic function
Concomitant comorbidities
Diet (rich in purines)

Abacavir/HLA-B*57:01



- The antiretroviral (ARV) **abacavir** is a nucleoside reverse transcriptase inhibitor (NRTI) used in combination with other ARV agents to treat HIV
- **Carriers of HLA-B*57:01 allele**
  - Increases hypersensitivity reaction (HSR) risk and can be life-threatening with repeat dosing
  - Symptoms of HSR include TWO of the following:
    - Fever
    - Rash
    - GI symptoms (N/V, abdominal pain)
    - Fatigue
    - Cough/dyspnea
- Prevalence of HLA-B*57:01 carriers vary by race
  - 2-3% among African Americans
  - 6-7% among Europeans
  - 20% Southwest Asians

Martin MA et al. *Clin Pharmacol Ther*. 2012; 91(4):734-8
https://www.pharmgkb.org/pathway/PA166104634 Accessed March 30, 2022

Abacavir/HLA-B*57:01

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. Choice of ART during pregnancy should be guided by recommendations from the Perinatal Guidelines.

INSTI plus 2 NRTIs:

- BIC/TAF/FTC **(AI)**[a]
- DTG/ABC/3TC **(AI)—if HLA-B*5701 negative**
- DTG plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)**

Triumeq®

INSTI plus 1 NRTI:

- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/ AdultandAdolescentGL.pdf. Accessed [March 30, 2022]

Abacavir PGx: HLA Factors

HLA Factor	Variant Allele	Allele Function	Examples of Medications	CPIC Level	PharmGKB Level of Evidence
HLA-B*57:01 [rs2395029]	Carrier	Increased risk of hypersensitivity	Abacavir	A	1A
	Non-carrier	Reduced risk of hypersensitivity			

Martin MA et al. *Clin Pharmacol Ther*. 2012; 91(4):734-8

Therapeutic Recommendations for Abacavir Use

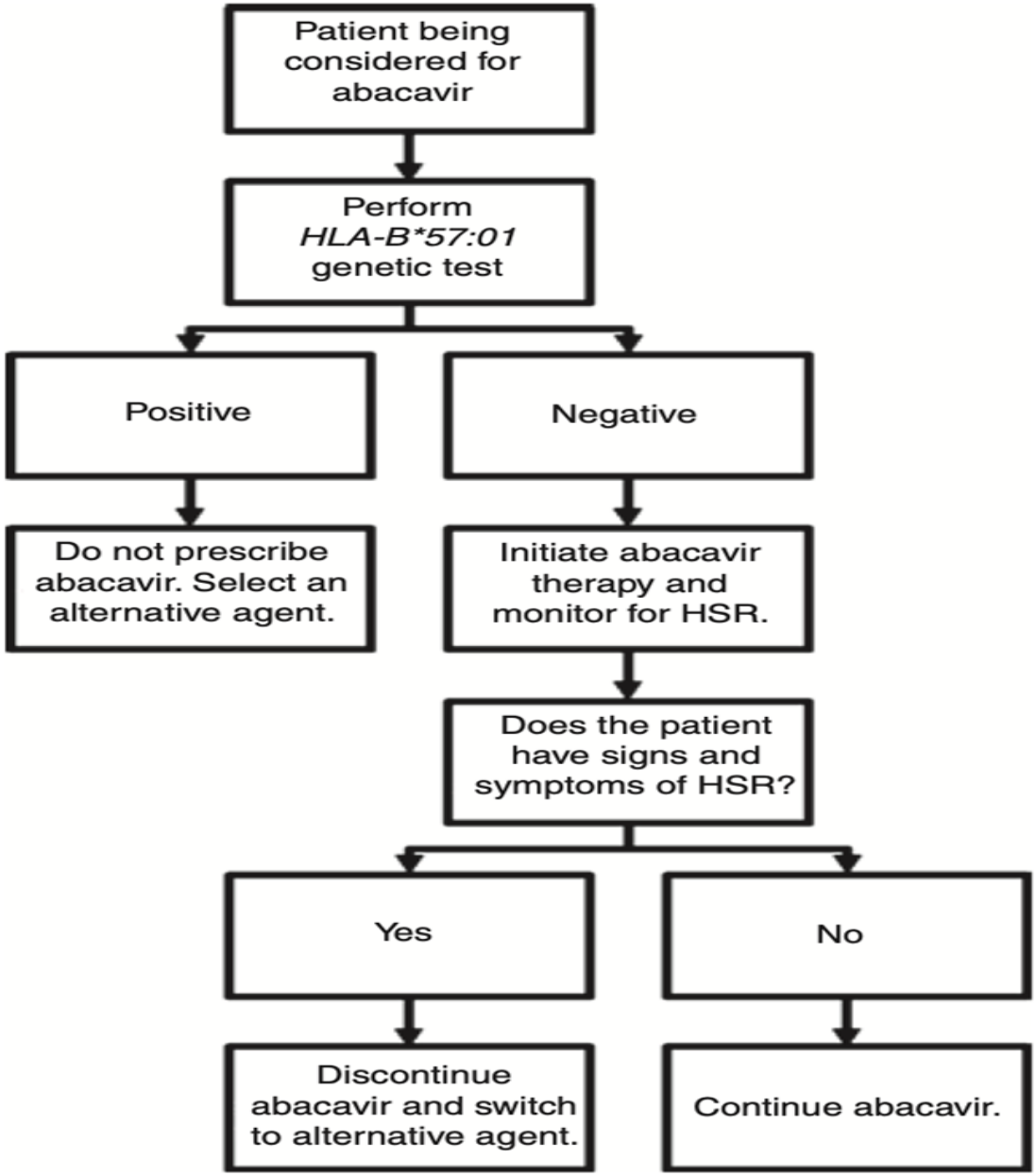
Table 2 Recommended therapeutic use of abacavir in relation to *HLA-B* genotype

Genotype	Implications for phenotypic measures	Recommendations for abacavir	Classification of recommendations[a]
Noncarrier of *HLA-B*57:01*	Low or reduced risk of abacavir hypersensitivity	Use abacavir per standard dosing guidelines	Strong
Carrier of *HLA-B*57:01*	Significantly increased risk of abacavir hypersensitivity	Abacavir is not recommended	Strong

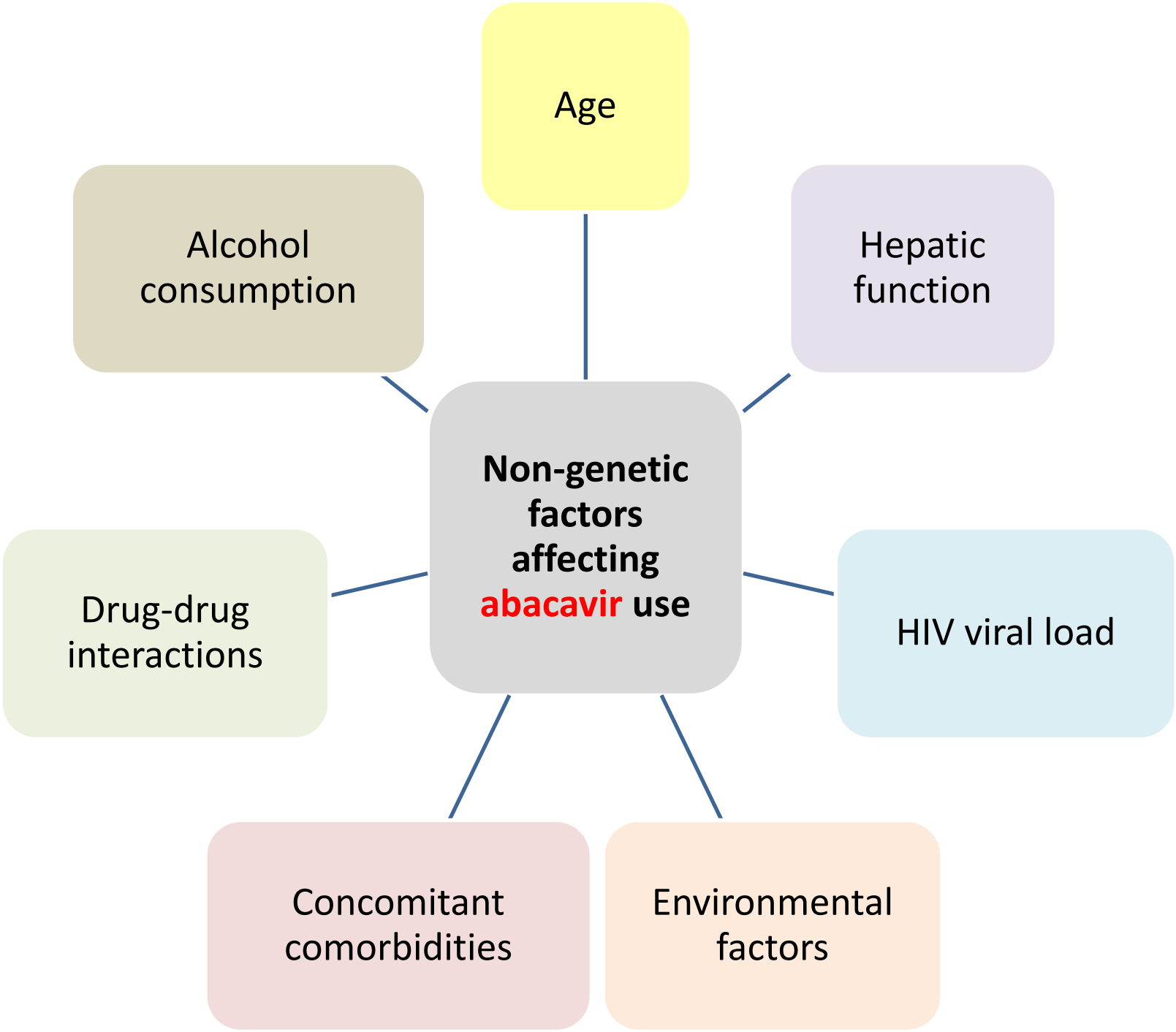
HLA-B, human leukocyte antigen B.

Martin MA et al. *Clin Pharmacol Ther*. 2012; 91(4):734-8

PGx Guided Algorithm for Abacavir Use



Martin MA et al. *Clin Pharmacol Ther*. 2012; 91(4):734-8


Age
Alcohol consumption
Hepatic function
Non-genetic factors affecting abacavir use
Drug-drug interactions
HIV viral load
Concomitant comorbidities
Environmental factors

PGx Testing Recommendations for Allopurinol and Abacavir Use

Drug	PharmGKB's interpretation of level of action implied in FDA label	FDA Table of PGx Associations
Allopurinol		
HLA-B*58:01	Testing recommended	Results in higher adverse reaction risk (severe skin reactions).
Abacavir		
HLA-B*57:01	Testing required	Results in higher adverse reaction risk (hypersensitivity reactions). Do not use abacavir in patients positive for HLA-B*57:01.

https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations Accessed March 30, 2022.
https://www.pharmgkb.org/labelAnnotation/PA166234701 Accessed March 30, 2022
https://www.pharmgkb.org/labelAnnotation/PA166104833 Accessed March 30, 2022

PGx Testing Recommendations for Allopurinol Use/American College of Rheumatology Guidelines

Annotation of ACR Guideline for allopurinol and HLA-B

Summary

HLA-B*58:01-positive individuals (those with the HLA-B*58:01 variant allele) should be prescribed an alternative drug to allopurinol.

Annotation

The **American College of Rheumatology** guidelines for the management of gout include the following statement about pharmacogenomic testing for HLA-B*58:01 and allopurinol:

> Those with HLA-B*5801 and of Korean descent with stage 3 or worse CKD (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 AHS, marked by HLA-B*5801 hazard ratios of several hundred. Such high-risk individuals were recommended to be prescribed an alternative to allopurinol if HLA-B*5801 positive.

excerpted from 2012 American College of Rheumatology Guidelines for the Management of Gout. Part1

https://www.pharmgkb.org/chemical/PA448320/guidelineAnnotation/PA166104993 Accessed March 30, 2022

Patient Case Example

- **CC:** DM is a 46 year old Asian male who presents to the clinic with severe pain and redness in the big toe for the past 24-36 hours. He tried taking some acetaminophen to manage some of the pain but has had no relief.
- **PMH:** occasional GERD
- **SH:** enjoys a good brisket dinner two times a week at his favorite BBQ place and drinks 2 beers/night. Denies recreational drug use and smoking. Exercises once a week.
- **Current medications:** occasionally will take some Maalox to offset some of his reflux
- **Vitals:** 90 kg, BP 128/82, HR 74, RR 16
- **Current labs:** WNL except uric acid = 8.2 mg/dL.
- **PGx test results** (available on next slide)

Manchester University

FOR ACADEMIC PURPOSES ONLY - NOT FOR CLINICAL USE

REPORT NUMBER-15871	SPECIMEN DETAILS	ORDERED BY

SPECIMEN TYPE: Buccal Swab

DM's PGx Testing Results

Test Details

Gene	Genotype	Phenotype	Alleles Tested
CYP2C19	*1/*7	Intermediate Metabolizer	*2, *3, *4, *4B, *5, *6, *7, *8, *9, *17
CYP2D6	*1/*1	Normal Metabolizer	*2, *3, *4, *4M, *6, *7, *8, *9, *10, *12, *14A, *14B, *17, *29, *35, *41
CYP3A5	*3/*3	Poor Metabolizer	*1D, *2, *3, *3B, *3C, *6, *7, *8, *9
CYP3A4	*1/*1	Normal Metabolizer	*1B, *2, *3, *12, *17, *22
VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity	-1639G>A
CYP4F2	*1/*3	Decreased Function	*2, *3
CYP2C9	*1/*3	Intermediate Metabolizer	*2, *3, *4, *5, *6, *11
CYP2B6	*1/*1	Normal Metabolizer	*6, *9
CYP1A2	*1A/*1F	Normal Metabolizer - Higher Inducibility	*1C, *1D, *1F, *1K, *1L, *1V, *1W
SLCO1B1	521T>C T/T	Normal Function	521T>C, 388A>G
CFTR	F508del/F508del	Negative	Numerous
DPYD	*1/*1	Normal Metabolizer	Numerous
TPMT	*1/*1	Normal Metabolizer	*2, *3A, *3B, *3C, *4
NUDT15	*1/*1	Normal Metabolizer	*2, *3, *4, *5, *6, *7, *8, *9
UGT1A1	*1/*1	Normal Metabolizer	*6, *27, *28, *36, *37, *60, *80
G6PD	B or B/B	Normal	Numerous

Additional Test Results (added to this original report)

HLA-B*15:02	negative/negative	Negative
HLA-B*57:01	negative/negative	Negative
HLA-B*58:01	negative/positive	Positive
HLA-A*31:01	negative/negative	Negative

Patient Case Example

Given DM's PGx testing results which of the following treatment choices would you recommend for managing DM's acute symptoms of gout?

a. Initiate allopurinol
b. Initiate colchicine
c. Initiate meloxicam (using normal starting dose)
d. Initiate acetaminophen (using higher dosing)

Benefits of PGx testing when considering allopurinol and abacavir use

Allopurinol (HLA-B*58:01)

- Reduce risk for allopurinol induced SCAR in high-risk populations

Abacavir (HLA-B*57:01)

- Reduce the incidence of abacavir induced hypersensitivity reaction
- Helps guide appropriate use of initial antiretroviral therapy
- *Incidental findings*
  - **HLA-B*57:01 has been overrepresented in HIV long-term non-progressors (LTNP)** [i.e. individuals who maintain a high CD4 cell count and low viral in the absence of antiretroviral therapy]
  - Associated with a lower viral load set point
  - Host immune response is able to control HIV more effectively

Martin MA et al. *Clin Pharmacol Ther*. 2012; 91(4):734-8

HLA-associated immune-mediated adverse drug reactions

Drug (references)	*HLA* allele	Adverse reaction	Prevalence of ADR	Carriage rate (%) of *HLA* allele[a]	OR	NPV (population)	PPV (population)	NNT
Abacavir (46, 47, 110, 137)	*B*57:01*	Hypersensitivity reaction	8% of population (3% true, 2–7% false positive HSR)	5–8 (European) <1 (Sub-Saharan African) <1 (Southeast Asian) 2–3 (African American)	960	100%	55%	13
Allopurinol (58, 129, 138–145)	*B*58:01*	SJS/TEN; DRESS/DIHS	1–4/1,000	1–6 (European) 10 (Sub-Saharan African) 10–15 (Southeast/ South Asian) 4 (African American)	580	100% (Han Chinese)	3% (Han Chinese)	250
Carbamazepine (50, 109, 117–120, 146–151)	*B*15:02*	SJS/TEN	<1–6/1,000	<0.1 (European) 10–15 (Southeast Asian) <1 (African)	>1,000	100% (Southeast Asian)	2–8%	1,000
Carbamazepine (54, 56, 112, 122, 152, 153)	*A*31:01*	DRESS/DIHS	0.05%	≤6 (European) <1 (Sub-Saharan African)	57.6	99.9%	0.89%	3,334
Oxcarbazepine (156–158)	*B*15:02*	SJS/TEN	Unknown	<0.1 (European) 10–15 (Southeast Asian) <1 African	27.9	99.9% (Han Chinese)	0.73% (Han Chinese)	>5,000

Karnes JH et al. *Annu Rev Pharmacol Toxicol*. 2019; 59:463–486.

SUMMARY TAKE HOME POINTS

- Carriers of HLA-B*15:02 may have an increased risk for drug-induced hypersensitivity reactions when initiating carbamazepine, oxcarbazepine and phenytoin
- Dose adjustments in maintenance phenytoin dosing are recommended for individuals who are *intermediate metabolizers (AS=1) and poor metabolizers* in CYP2C9
- Carriers of HLA-A*31:01 may have an increased risk for drug-induced hypersensitivity reactions when initiating carbamazepine
- Carriers of HLA-B*58:01 may have an increased risk for drug-induced hypersensitivity reactions when initiating allopurinol
- Carriers of HLA-B*57:01 may have an increased risk for drug-induced hypersensitivity reactions when initiating abacavir