Allele function assignment SOP and CYP2C9 function assignment

Table 2 Recommended dosing of phenytoin/fosphenytoin based on *HLA-B*15:02* and *CYP2C9* phenotype/genotype

	*HLA-B*15:02* carrier			*HLA-B*15:02* noncarrier		
Phenotype/ genotype	**Implication**	**Therapeutic recommendation**	**Classification of recommendation[a]**	**Implication**	**Therapeutic recommendation**	**Classification of recommendation[a]**
CYP2C9 extensive metabolizer	Increased risk of phenytoin-induced SJS/ TEN	If patient is phenytoin naive,[b] do not use phenytoin/ fosphenytoin[c]	Strong	Normal phenytoin metabolism	Initiate therapy with recommended maintenance dosed	Strong
CYP2C9 intermediate metabolizer	Increased risk of phenytoin-induced SJS/ TEN	If patient is phenytoin naive,[b] do not use phenytoin/ fosphenytoin[c]	Strong	Reduced phenytoin metabolism. Higher plasma concentrations will increase probability of toxicities	Consider 25% reduction of recommended starting maintenance dose.[d] Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response	Moderate
CYP2C9 poor metabolizer	Increased risk of phenytoin-induced SJS/ TEN	If patient is phenytoin naive,[b] do not use phenytoin/ fosphenytoin[c]	Strong	Reduced phenytoin metabolism. Higher plasma concentrations will increase probability of toxicities	Consider 50% reduction of recommended starting maintenance dose.[d] Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response	Strong

CYP, cytochrome P450; SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

[a]Rating scheme described in the **Supplementary Material** online. [b]If the patient has previously used phenytoin for longer than 3 months without incidence of cutaneous adverse reactions, reinitiate phenytoin with caution. Adjust dose based on *CYP2C9* genotype if known. [c]Carbamazepine should not be used as an alternative.[4] Alternative medications such as oxcarbazepine, eslicarbazepine acetate, and lamotrigine have some evidence linking SJS/TEN with the *HLA-B*15:02* allele, and thus caution should be used in choosing alternatives to phenytoin (see **Supplementary Material** online for details). [d]Recommended maintenance dose based on patient's clinical characteristics.

Table 1 Assignment of likely phenotype based on genotypes

Assignment of likely CYP2C9 phenotype based on genotype		
Likely phenotype[a]	**Genotype**	**Examples of diplotypes**
Extensive metabolizer (normal activity) (constitutes ~91% of patients)	An individual carrying two normal-function alleles	**1/*1*
Intermediate metabolizer (heterozygote or intermediate activity) (constitutes ~8% of patients)[c]	An individual carrying one normal-function allele plus one decreased-function allele	**1/*3, *1/*2*
Poor metabolizer (homozygous variant, low or deficient activity) (constitutes ~1% of patients)	An individual carrying two decreased-function alleles	**2/*2, *3/*3, *2/*3*

CPIC allele function SOP

- The goal is to assign “Allele Clinical Functional Status” to all alleles (or to isolated variants), using standardized terms.
  - Increased, normal, decreased, no, uncertain, unknown
- “CPIC Allele Clinical Function status” will be used to generate lists of clinically actionable variants
- If that variant were present in the right gene dosage (e.g. usually as part of a diplotype with another similarly actionable variant), prescribing decisions would be altered from the normal baseline prescribing actions.

New format for allele functionality table

GENE: TPMT	10/20/2017						
Allele	Activity Score (Optional)	Allele Functional Status (Optional)	Allele Clinical Functional Status (Required)	Allele Clinical Function Substrate Specificity (Optional)	PMID (Optional)	Strength of Evidence (Optional)	Findings (Optional)
*1			Normal Function				
*2			No Function		786267;16220112;9177237;18708949;864		
*3A			No Function		16220112;9177237;18708949;8644731;85 61894		
*3B			No Function		16220112;18708949;8644731;8561894		
*3C			No Function		16220112;18708949;8644731;8561894		
*4			No Function		9246020		
*5			Uncertain Function		18708949;16220112;9246020		

Description for Assignment of Allele Clinical Function to the allele vs categorizing as “uncertain”.

- Supportive evidence needed to assign function vs uncertain
  - **Definitive**: The role of this variant in this particular drug phenotype has been repeatedly demonstrated, and has been upheld over time.
  - **Strong**: The role of this variant in the drug phenotype has been independently demonstrated in at least two separate clinical studies providing **strong** supporting evidence for this variant’s role in drug phenotype and there is compelling variant-level evidence from different types of supporting experimental data.

Description for Assignment of Allele Clinical Function to the allele vs categorizing as “uncertain”.

- Supportive evidence needed to assign function vs uncertain
  - **Moderate:** There is **moderate** evidence to support a causal role for this variant in this drug phenotype, including both of the following types of evidence:
    - At least 2 patient cases evidence for drug phenotype causality
    - Some experimental data supporting the variant-drug phenotype association
  - **Limited**: There is **limited** evidence to support a causal role for this variant in this drug phenotype, such as:
    - Fewer than 2 patient cases
    - experimental or computational data supporting the variant-drug phenotype association
    - And no convincing evidence has emerged that contradicts the role of the variant in the noted drug phenotype.

Description for Assignment of Allele Clinical Function to the allele vs categorizing as “uncertain”.

- Supportive evidence needed to assign function vs uncertain
  - Inadequate evidence = uncertain function
    - Fewer than 2 patient cases with no convincing experimental data, or
    - fewer than 2 patient cases and extremely limited or conflicting experimental data.
- This designation should be used when the evidence is NOT strong enough to support a clinical functional status that can inform prescribing actionability.
- The threshold for what evidence is enough to inform actionability may differ for different genes.

New format for allele functionality table

GENE: TPMT	10/20/2017						
Allele	Activity Score (Optional)	Allele Functional Status (Optional)	Allele Clinical Functional Status (Required)	Allele Clinical Function Substrate Specificity (Optional)	PMID (Optional)	Strength of Evidence (Optional)	Findings (Optional)
*1			Normal Function				
*2			No Function		86267;16220112;9177237;18708949;864		
*3A			No Function		6220112;9177237;18708949;8644731;85 61894		
*3B			No Function		16220112;18708949;8644731;8561894		
*3C			No Function		16220112;18708949;8644731;8561894		
*4			No Function		9246020		
*5			Uncertain Function		18708949;16220112;9246020		

Allele functional status

- Expert panels have the option of also assigning “Allele Functional Status (not clinical)” to alleles.
- This is to accommodate data on allele function that is of interest, but the data do not rise to such a level that this status could be used for assessing clinical actionability in prescribing.
- This is a separate designation from the mandatory CPIC “Allele Clinical Function Status” (which is to be used for interpreting diplotypes into phenotypes and prescribing actionability), and this status will not be used for purposes of actionability in CPIC guidelines.

Allele Clinical Function Substrate Specificity

- Although there are always some data that are specific to one substrate and not to others, substrate-specific considerations in assigning allele function should be relatively uncommon for pharmacogenes.
- The Allele Definition, Allele Functionality, and Diplotype-to-Phenotype tables should be constructed assuming that an interpretation may be needed for each patient that is “substrate independent” (i.e. in the setting of preemptive genotyping, when a particular drug may not even yet be contemplated).
- However, the allele function table does allow for indicating which alleles have strong substrate specificity, such that different functions may be assigned to the allele with respect to drug A vs Drug B, and this information will be retrievable.
- Only when substrate specificity is so strong that it will impact interpretations of allele function and thereby affect prescribing recommendations for drug A vs drug B should it be noted in the allele function tables, with evidence supporting the particularly substrate specificity indicated in the row substrate specific function in the Allele Functionality Table.

CPIC® Guideline for Phenytoin and CYP2C9 and HLA-B

Most recent guideline publication:

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP2C9* and *HLA-B* Genotype and Phenytoin Dosing (November 2014)

Table 1 Assignment of likely phenotype based on genotypes

Assignment of likely CYP2C9 phenotype based on genotype		
Likely phenotype[a]	**Genotype**	**Examples of diplotypes**
Extensive metabolizer (normal activity) (constitutes ~91% of patients)	An individual carrying two normal-function alleles	**1/*1*
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Poor metabolizer (homozygous variant, low or deficient activity) (constitutes ~1% of patients)	An individual carrying two decreased-function alleles	**2/*2, *3/*3, *2/*3*

Table 2 Recommended dosing of phenytoin/fosphenytoin based on *HLA-B*15:02* and *CYP2C9* phenotype/genotype

	*HLA-B*15:02* carrier			*HLA-B*15:02* noncarrier		
Phenotype/ genotype	**Implication**	**Therapeutic recommendation**	**Classification of recommendation[a]**	**Implication**	**Therapeutic recommendation**	**Classification of recommendation[a]**
CYP2C9 extensive metabolizer	Increased risk of phenytoin-induced SJS/ TEN	If patient is phenytoin naive,[b] do not use phenytoin/ fosphenytoin[c]	Strong	Normal phenytoin metabolism	Initiate therapy with recommended maintenance dosed	Strong
CYP2C9 intermediate metabolizer	Increased risk of phenytoin-induced SJS/ TEN	If patient is phenytoin naive,[b] do not use phenytoin/ fosphenytoin[c]	Strong	Reduced phenytoin metabolism. Higher plasma concentrations will increase probability of toxicities	Consider 25% reduction of recommended starting maintenance dose.[d] Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response	Moderate
CYP2C9 poor metabolizer	Increased risk of phenytoin-induced SJS/ TEN	If patient is phenytoin naive,[b] do not use phenytoin/ fosphenytoin[c]	Strong	Reduced phenytoin metabolism. Higher plasma concentrations will increase probability of toxicities	Consider 50% reduction of recommended starting maintenance dose.[d] Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response	Strong

CYP, cytochrome P450; SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

[a]Rating scheme described in the **Supplementary Material** online. [b]If the patient has previously used phenytoin for longer than 3 months without incidence of cutaneous adverse reactions, reinitiate phenytoin with caution. Adjust dose based on *CYP2C9* genotype if known. [c]Carbamazepine should not be used as an alternative.[4] Alternative medications such as oxcarbazepine, eslicarbazepine acetate, and lamotrigine have some evidence linking SJS/TEN with the *HLA-B*15:02* allele, and thus caution should be used in choosing alternatives to phenytoin (see **Supplementary Material** online for details). [d]Recommended maintenance dose based on patient's clinical characteristics.

CYP2C9/phenytoin

Type of experimental model (in vitro, in vivo preclinical, or clinical)	Major findings	References from 2014 (2014 guideline supplement reference number (PMID:))	Level of evidence* (2014)
In vitro	CYP2C9*2 results in a 29% reduction in phenytoin clearance as compared with *1	36	Moderate
In vitro	CYP2C9*3 results in a 93-95% reduction in phenytoin clearance as compared with *1	36, 38	Moderate

Table 4 Comparing wild and mutant genotypes of CYP2C9*2 for dose (mg/kg) and drug level (mcg/ml)

Variables	CC ($n = 81$)	CT ($n = 8$)	P value
Dose (mean ± SD)	5.2 ± 1.15	5.1 ± 0.95	0.89
Phenytoin level[a] (median)	6.8	9.5	0.74

[a]Non parametric test applied as variability was high (Wilcoxon rank-sum test)

Table 5 Comparing wild and mutant genotypes of CYP2C9*3 for dose (mg/kg) and drug level (mcg/ml)

Variables	AA ($n = 71$)	AC ($n = 18$)	P value
Dose (mean ± SD)	5.3 ± 1.20	4.8 ± 0.69	0.12
Phenytoin level[a] (Median)	5.9	18.8	0.009

[a]Non parametric test applied as variability was high (Wilcoxon rank-sum test)

BMC Pediatr. 2016 May 14;16:66. doi: 10.1186/s12887-016-0603-0.

CYP2C9/celecoxib

Clinical	CYP2C9*3 is associated with drastically decreased celecoxib metabolism (increased celecoxib plasma concentration and decreased oral clearance).	Tang 2001	11337938	High
		Brenner 2003	12603175	
		Kirchheiner 2003	12893985	
		Fries 2006	16401468	
		Lundblad 2006	16513453	
		Prieto-PÃ©rez 2013	23996211	
		Liu 2015	26360837	
		Kim 2017	27864660	
		Stempak 2005	16153401	
		Kusama 2009	19082874	
Clinical	CYP2C9*2 is NOT associated with decreased celecoxib metabolism (increased celecoxib plasma concentration and decreased oral clearance).	Tang 2001	11337938	High
		Brenner 2003	12603175	
		Kirchheiner 2003	12893985	
		Fries 2006	16401468	
		Prieto-PÃ©rez 2013	23996211	
		Kusama 2009	19082874	

Table 1 Recommended daily warfarin doses (mg/day) to achieve a therapeutic INR based on *CYP2C9* and *VKORC1* genotype using the warfarin product insert approved by the US Food and Drug Administration

VKORC1: –1639G>A	*CYP2C9*1/*1*	*CYP2C9*1/*2*	*CYP2C9*1/*3*	*CYP2C9*2/*2*	*CYP2C9*2/*3*	*CYP2C9*3/*3*
GG	5–7	5–7	3–4	3–4	3–4	0.5–2
GA	5–7	3–4	3–4	3–4	0.5–2	0.5–2
AA	3–4	3–4	0.5–2	0.5–2	0.5–2	0.5–2

Reproduced from updated warfarin (Coumadin) product label.

Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Kelly E. Caudle, PharmD, PhD[1], Henry M. Dunnenberger, PharmD[2], Robert R. Freimuth, PhD[3], Josh F. Peterson, MD[4,5], Jonathan D. Burlison, PhD[1], Michelle Whirl-Carrillo, PhD[6], Stuart A. Scott, PhD[7], Heidi L. Rehm, PhD[8], Marc S. Williams, MD[9], Teri E. Klein, PhD[6], Mary V. Relling, PharmD[1], James M. Hoffman, PharmD, MS[1]

Table 2 Final consensus terms for allele functional status and phenotype

Term/gene				Example
drug-metabolizing enzymes (CYP2C19, CYP2D6, CYP3A5, CYP2C9, TPMT, DPYD, UGT1A1)		rapid metabolizers	than 2 normal function alleles	*CYP2D6*1/*1XN*
	Rapid metabolizer	Increased enzyme activity compared to normal metabolizers but less than ultrarapid metabolizers	Combinations of normal function and increased function alleles	*CYP2C19*1/*17*
	Normal metabolizer	Fully functional enzyme activity	Combinations of normal function and decreased function alleles	*CYP2C19*1/*1*
	Intermediate metabolizer	Decreased enzyme activity (activity between normal and poor metabolizer)	Combinations of normal function, decreased function, and/or no function alleles	*CYP2C19*1/*2*
	Poor metabolizer	Little to no enzyme activity	Combination of no function alleles and/or decreased function alleles	*CYP2C19*2/*2*

When both alleles have no function, the phenotype of the patient is “poor metabolizer” or lowest level of phenotype. When patient has one “no function” allele and one “normal function” allele, they are intermediate metabolizers. It is recognized that most “no function” alleles have some low level of function, so this is a relative term.

Summary from 1st call

- *2 and *3 have different levels of function
- *3/*3 is the closest to PM diplotype (with more evidence) so should be categorized as a “no function”
- *1/*3 would be IM (one no function plus one normal function)
- *2 should categorized as “decreased function”

What we had to decide

- *2/*3 (one decreased function plus one no function = PM or IM)
- *1/*2 (one normal function plus one decreased function = IM or NM)
- *2/*2: IM?
- What about other alleles? Can they be grouped accordingly?

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types instead of the sum of alleles, could the regression be improved. This result is consistent

Table 1. CYP2C9 genotypes and respective measured and estimated metabolic ratios for flurbiprofen.

		MR Measured		MR Estimated	
Genotype	**Number/frequency**	**MR (mean ± SD)**	**Percent of wild type activity**	**MR (estimate ± SE)**	**Percent of wild type activity**
CYP2C9*1/*1	181/64.0%	1.189 ± 0.314	= 100	1.192 ± 0.021	= 100
CYP2C9*1/*2	52/18.4%	1.005 ± 0.202	85	1.001 ± 0.033	84
CYP2C9*1/*3	39/13.8%	0.728 ± 0.256	61	0.709 ± 0.041	60
CYP2C9*2/*2	5/1.8%	0.834 ± 0.284	70	0.810 ± 0.066	68
CYP2C9*2/*3	5/1.8%	0.424 ± 0.095	36	0.518 ± 0.052	43
CYP2C9*3/*3	1/0.4%	0.096 single value	8	0.226 ± 0.084	19

Estimated allelic contributions: 0.596±0.010, 0.405±0.033, and 0.113±0.042 for CYP2C9*1, *2 and *3, respectively.

SD, standard deviation; SE, standard error; MR, metabolic ratio.

doi:10.1371/journal.pone.0120403.t001

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	*1/*1		*1/*2		*1/*3		*2/*2		*2/*3		*3/*3		ref
Celecoxib	1	[10]	1.17	[5]	0.65	[4]	0.84	[2]	–	–	1.09	[1]	(84)
	1	[4]	–	–	0.66	[4]	–	–	–	–	0.30	[3]	(85)
	1	[12]	1.01	[2]	0.40	[2]	–	–	–	–	0.23	[1]	(25)
Mean[b]	1	[26]	1.12	[7]	0.60	[10]	0.84	[2]	–	–	0.45	[5]	
Diclofenac	1	[10]	1.08	[6]	1.30	[4]	0.58	[2]	–	–	1.39	[1]	(84)
	1	[3]	1.42	[4]	1.11	[4]	1.47	[3]	2.02	[3]	1.14	[3]	(18)
	1	[6]	–	–	1.36	[6]	–	–	–	–	–	–	(86)
	1	[6]	0.62	[3]	0.68	[5]	1.13	[1]	0.52	[4]	1.36	[1]	(87)
Mean[b]	1	[25]	1.08	[13]	1.11	[19]	1.12	[6]	1.16	[7]	1.23	[5]	
S-flurbiprofen	1	[5]	0.73	[5]	0.56	[5]	–	–	–	–	–	–	(88)
Losartan [E3174 formation]	1	[5]	0.50	[5]	0.72	[5]	0.85	[1]	–	–	–	–	(36)
	1	[6]	0.56	[3]	0.57	[5]	0.62	[3]	0.23	[4]	0.01	[1]	(17)
Mean[b]	1	[11]	0.52	[8]	0.64	[10]	0.68	[4]	0.23	[4]	0.01	[1]	
S-phenprocoumon	1	[7]	0.78	[4]	0.82	[5]	0.69	[3]	0.49	[4]	0.63	[3]	(89)
Phenytoin	1	[68]	0.75	[13]	0.74	[16]	0.63	[3]	–	–	0.70	[1]	(90)
	1	[18]	0.67	[7]	0.68	[4]	0.37	[1]	0.37	[1]	–	–	(91)
	1	[37]	0.60	[9]	0.70	[9]	0.69	[3]	0.42	[2]	–	–	(92)
	1	[151]	–	–	0.690	[18]	–	–	–	–	–	–	(93)
Mean[b]	1	[274]	0.70	[29]	0.71	[47]	0.62	[7]	0.40	[3]	0.70	[1]	
Tolbutamide	1	[15]	0.91	[7]	0.71	[3]	0.67	[1]	–	–	–	–	(94)
	1	[6]	0.89	[4]	0.58	[4]	0.77	[3]	0.46	[3]	0.15	[3]	(95)
	1	[5]	0.71	[5]	0.52	[5]	–	–	–	–	–	–	(96)
	1	[12]	–	–	0.75	[6]	–	–	–	–	–	–	(97)
Mean[b]	1	[38]	0.84	[16]	0.64	[18]	0.75	[4]	0.46	[3]	0.15	[3]	
Torsemide	1	[12]	0.98	[9]	0.54	[9]	0.59	[1]	0.44	[3]	0.22	[2]	(98)
	1	[80]	–	–	–	–	0.96	[15]	–	–	0.33	[2]	(99)
Mean[b]	1	[92]	0.98	[9]	0.54	[9]	0.94	[16]	0.44	[3]	0.33	[4]	
S-warfarin	1	[118]	0.66	[32]	0.58	[27]	0.55	[2]	0.31	[6]	0.12	[3]	(100)
	1	[74]	0.73	[30]	0.50	[15]	–	–	–	–	–	–	(101)
	1	[54]	0.58	[15]	0.52	[16]	0.32	[2]	0.23	[4]	0.09	[2]	(16)
	1	[42]	–	–	0.34	[4]	–	–	–	–	0.10	[1]	(62)
Mean[b]	1	[288]	0.67	[77]	0.53	[62]	0.44	[4]	0.28	[10]	0.11	[6]	

Table V. Summary of $CL_{oral}R^{a}$ value of each diplotype from literature data (presented as $CL_{oral}R$ [number of subjects])

	*1/*1		*1/*2		*1/*3		*2/*2		*2/*3		*3/*3		ref
Celecoxib	1	[10]	1.17	[5]	0.65	[4]	0.84	[2]	–	–	1.09	[1]	(84)
	1	[4]	–	–	0.66	[4]	–	–	–	–	0.30	[3]	(85)
	1	[12]	1.01	[2]	0.40	[2]	–	–	–	–	0.23	[1]	(25)
Mean[b]	1	[26]	1.12	[7]	0.60	[10]	0.84	[2]	–	–	0.45	[5]	
Diclofenac	1	[10]	1.08	[6]	1.30	[4]	0.58	[2]	–	–	1.39	[1]	(84)
	1	[3]	1.42	[4]	1.11	[4]	1.47	[3]	2.02	[3]	1.14	[3]	(18)
	1	[6]	–	–	1.36	[6]	–	–	–	–	–	–	(86)
	1	[6]	0.62	[3]	0.68	[5]	1.13	[1]	0.52	[4]	1.36	[1]	(87)
Mean[b]	1	[25]	1.08	[13]	1.11	[19]	1.12	[6]	1.16	[7]	1.23	[5]	
S-flurbiprofen	1	[5]	0.73	[5]	0.56	[5]	–	–	–	–	–	–	(88)

Table V. Summary of $CL_{oral}R^{a}$ value of each diplotype from literature data (presented as $CL_{oral}R$ [number of subjects])

	*1/*1		*1/*2		*1/*3		*2/*2		*2/*3		*3/*3		ref
Phenytoin	1	[68]	0.75	[13]	0.74	[16]	0.63	[3]	–	–	0.70	[1]	(90)
	1	[18]	0.67	[7]	0.68	[4]	0.37	[1]	0.37	[1]	–	–	(91)
	1	[37]	0.60	[9]	0.70	[9]	0.69	[3]	0.42	[2]	–	–	(92)
	1	[151]	–	–	0.690	[18]	–	–	–	–	–	–	(93)
Mean[b]	1	[274]	0.70	[29]	0.71	[47]	0.62	[7]	0.40	[3]	0.70	[1]	

Table V. Summary of $CL_{oral}R^{a}$ value of each diplotype from literature data (presented as $CL_{oral}R$ [number of subjects])

	*1/*1		*1/*2		*1/*3		*2/*2		*2/*3		*3/*3		ref
S-warfarin	1	[118]	0.66	[32]	0.58	[27]	0.55	[2]	0.31	[6]	0.12	[3]	(100)
	1	[74]	0.73	[30]	0.50	[15]	–	–	–	–	–	–	(101)
	1	[54]	0.58	[15]	0.52	[16]	0.32	[2]	0.23	[4]	0.09	[2]	(16)
	1	[42]	–	–	0.34	[4]	–	–	–	–	0.10	[1]	(62)
Mean[b]	1	[288]	0.67	[77]	0.53	[62]	0.44	[4]	0.28	[10]	0.11	[6]	

Warfarin dose

- recent meta-analysis by Lindh et al.
  - 39 studies and 7907 patients:
  - CYP2C9*1/*2 -- 19.6% lower than dose required for *1/*1
  - CYP2C9*1/*3 -- 33.7% lower than dose required for *1/*1
  - CYP2C9*2/*2 -- 36.0% lower than dose required for *1/*1
  - CYP2C9*2/*3 -- 56.7% lower than dose required for *1/*1
  - CYP2C9*3/*3 -- 78.1% lower than dose required for *1/*1

Siponimod: Genotype-based dosing

CYP2C9 genotype groups	
*1/*1;*1/*2;*2/*2	Standard maintenance dose: 2 mg
*1/*3; *2/*3	Lower maintenance dose: 1 mg
*3/*3	**Contraindicated**

Siponimod is extensively metabolized, mainly via CYP2C9 (79.3%), followed by CYP3A4 (18.5%)

Drug exposure is significantly affected in patients who carry one or two copies of *3

Likely Phenotype	Activity Score	Genotypes	Examples of diplotypes
Normal metabolizer	2	An individual carrying two normal function alleles	*1/*1
Intermediate metabolizer	1	An individual carrying one normal function allele plus one no function allele	*1/*3
		two decreased function alleles	*2/*2
	1.5	one normal function allele plus one decreased function allele	*1/*2
Poor metabolizer	0.5	one no function allele plus one decreased function allele	*2/*3
	0	An individual carrying two no function alleles	*3/*3

CYP2C9 CPIC clinical allele function status

- Authors were assigned alleles to review and we discussed all alleles on a conference call
  - Decreased function alleles-closer to *2 or *3 function (decreased vs no function vs unclear)?
  - Assigned strength of evidence

Need feedback

- If are interested in providing feedback on the SOP, please email Kelly.caudle@stjude.org.

- Plan to write-up SOP for publication.