

Final Consensus *CYP2D6* genotype to phenotype table-March 2019

After 6 surveys (see surveys and project details [here](#)), the CYP2D6 experts have reached consensus (see **Table** below). Below we also highlight the rationale for major changes to the current CPIC CYP2D6 genotype to phenotype table.

Rationale of downgrading an Activity Score (AS) of 1 to the IM group:

- 1) Experts were more in favor of this option albeit very close (41% vs 38%).
 - a. The option of classifying AS=1 as IM appears to be more likely to be accepted across all interest groups compared to a method that creates a new phenotype group for AS=0.5.
- 2) After a consensus is reached, the recommendation for clinical labs would be to utilize this standardized classification.
 - a. Based on our survey results, laboratory experts were more in favor of classifying AS of 0.5 to 1 as CYP2D6 IMs than creating a new phenotype group.
 - b. More reporting labs currently classify AS of 0.5 to 1 as CYP2D6 IMs (**Table 2**).
- 3) Recommendations from CPIC could be different for AS \leq 1 if needed.
- 4) Published studies vary on how they group activity scores for comparison. Some studies compare AS of 0.5-1 vs 2 while others compare AS of 1 vs 2. Classifying an AS of 1 as IM can be viewed as a more conservative approach guiding therapy, however, this grouping may not reveal potentially important differences among AS of 0.25, 0.5 and 1.

Rationale for downgrading *CYP2D6*10* from 0.5 to 0.25:

- 1) *CYP2D6*10* has been characterized as an allele conveying decreased function for a number of substrates. Although its activity ranges, it appears to be, in average, considerably lower compared to other decreased function alleles.
- 2) The activity for subjects with *CYP2D6*10/*10* (AS=1) or **10/no function* (AS=0.5) diplotypes may therefore be over-estimated even when an AS of 1 is classified as IM.
- 3) Assigning a value of 0.25 to the *CYP2D6*10* allele for AS calculation will group **10/*10* as AS=0.5 and **10/no function* as AS=0.25; the former will still be classified as IM, but would be in a group for which CPIC may identify a special recommendation. The introduction of a value of 0.25 creates the option of grouping subjects with an AS=0.25 with severely reduced activity as PMs.

Rational for AS of 2.25 assignment as CYP2D6 Normal Metabolizer:

- 1) The majority of experts agreed to downgrade *CYP2D6*10* due to considerable reduction in activity. A *CYP2D6*2x2/*10* genotype (AS 2.25), for example, would be categorized

as a normal metabolizer with the assumption that *CYP2D6*10* does not contribute clinically appreciable activity to the overall function.

CYP2D6 Genotype to Phenotype table (current vs new)					
Likely phenotype	CURRENT CPIC activity score definition	CURRENT DPWG activity score definition	PROPOSED NEW standardized activity score definition	With no gaps PM=0	Examples of CYP2D6 diplotypes for new system
CYP2D6 ultrarapid metabolizer	>2	>2.5	>2.25	>2.25	*1/*1xN, *1/*2xN, *2/*2xN, *2x2/*9
CYP2D6 normal metabolizer	1-2	1.5-2.5	1.25 1.5 2.0 2.25	$1.25 \leq x \leq 2.25$	*1/*1, *1/*2, *1/*9, *1/*41, *2/*2, *1/*10, *2x2/*10
CYP2D6 intermediate metabolizer	0.5	0.5-1	0.25 0.5 0.75 1	$0 < x < 1.25$	*4/*10, *4/*41, *1/*5, *10/*10, *41/*41
CYP2D6 poor metabolizer	0	0	0	0	*3/*4, *4/*4, *5/*5, *5/*6

Feedback

The final proposed standardized activity score definitions were posted for public comment for two months. In short, we received feedback on some points of which two needed to be addressed.

- 1) Adding a Rapid Metabolizer group
- 2) Continuous scale for activity score (no gaps)

After two additional surveys, experts decided against the addition of a rapid metabolizer phenotype based on limited data to support this group (limited studies exist that differentiate between activity scores greater than 2 (e.g., AS of 2 vs AS of 3)). However, experts agreed to add a continuous scale for activity score (see table above).

Other alleles that contain the *CYP2D6*10* function-defining SNP (100C>T; rs1065852)

There are other alleles that contain the *CYP2D6*10* function-defining SNP (100C>T; rs1065852) in combination with other SNP(s) known to not impact function (e.g. 4180G>G) or decrease function on their own (e.g. 1023C>T) which are currently classified by CPIC as "uncertain" (see

table below). Some experts recommended that these alleles should also be downgraded to an activity value of 0.25; however, after survey 6 and concerns from some the *CYP2D6* experts that not enough evidence exists at this time to downgrade all of these alleles, those containing the *CYP2D6**10 function-defining SNP (100C>T; rs1065852) will be assessed as part of the CPIC guideline development process and functional status assigned at that time.

Allele	Current CPIC function	AA change causing variants
*10	decreased	100C>T; 4180G>C
*49	decreased	100C>T; 1611T>A; 4180G>C
*54	decreased	100C>T; 2556C>T; 4180G>C
*65	decreased	100C>T; 2850C>T; 4180G>C
*72	decreased	100C>T; 3318G>A; 4180G>C
*37	uncertain	100C>T; 1943G>A; 4180G>C
*52	uncertain	100C>T; 3877G>A; 4180G>C
*64	uncertain	100C>T; 1023C>T; 4180G>C
*87	uncertain	14C>T; 100C>T; 4180G>C
*94	uncertain	100C>T; 3181A>G; 4180G>C
*95	uncertain	100C>T; 3334A>C; 4180G>C