

Final Consensus CYP2D6 genotype to phenotype table

We are seeking feedback on the final CYP2D6 genotype to phenotype table. Please email any comments to contact@cpicpgx.org by September 20th. Please make sure to read the following carefully as it contains the rationale for each change made to the current system CPIC now uses.

After 6 surveys (see surveys and project details [here](#)) has all survey results posted for review), 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 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=0.5 and 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 0.5 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* function contributes very little to the overall function.

CYP2D6 Genotype to Phenotype table (current vs new)				
Likely phenotype	CURRENT CPIC activity score definition	CURRENT DPWG activity score definition	NEW standardized activity score definition	Examples of CYP2D6 diplotypes for new system
CYP2D6 ultrarapid metabolizer	>2	>2.5	> 2.25	*1/*1xN, *1/*2xN, *2/*2xN, *2x2/*9
CYP2D6 normal metabolizer	1-2	1.5-2.5	1.25-2.25	*1/*1, *1/*2, *1/*9, *1/*41, *2/*2, *1/*10, *2x2/*10
CYP2D6 intermediate metabolizer	0.5	0.5-1	0.25-1	*4/*10, *4/*41, *1/*5, *10/*10, *41/*41
CYP2D6 poor metabolizer	0	0	0	*3/*4, *4/*4, *5/*5, *5/*6

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, the alleles that contain 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