

## 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](mailto:contact@cpicpgx.org) by October 26th. 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) genotypes 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.

Likely phenotype	CURRENT CPIC activity score definition	CURRENT DPWG activity score definition	NEW standardized activity score definition	Examples of <i>CYP2D6</i> diplotypes for new system
CYP2D6 ultrarapid metabolizer	>2	>2.5	> 2.25	*1/*1x3
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.

<b>Allele</b>	<b>Current CPIC function</b>	<b>AA change causing variants</b>
*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