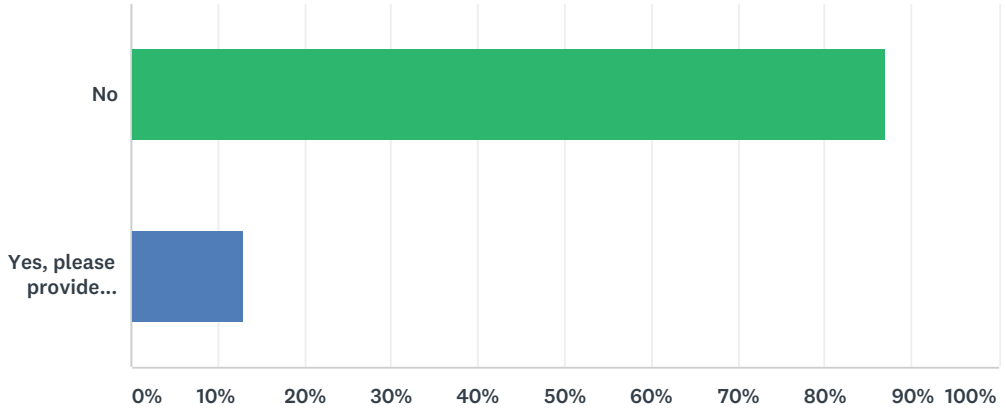
Q1 Are you in favor of adding a CYP2D6 Rapid Metabolizer phenotype group?

Answered: 23 Skipped: 0



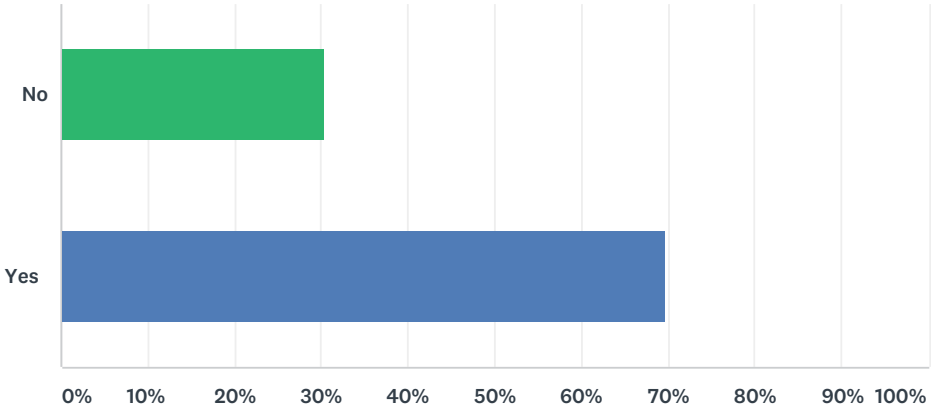
ANSWER CHOICES	RESPONSES	
No	86.96%	20
Yes, please provide rational and/or references to support an additional phenotype group for CYP2D6.	13.04%	3
TOTAL		23

#	YES, PLEASE PROVIDE RATIONAL AND/OR REFERENCES TO SUPPORT AN ADDITIONAL PHENOTYPE GROUP FOR CYP2D6.	DATE
1	I am in favor of a Rapid Metabolizer group so moving forward patients with this potential phenotype can be analyzed as a separate group; the lack of evidence for a RM phenotype also comes from pooling of phenotypes therefore not allowing to distinguish if a drug response may be different. I agree that the added group may end up not being relevant for all substrates; but since there is still much to learn, having distinct phenotype categories that serve as standard for clinical trials is scientifically more rigorous.	1/7/2019 11:44 PM
2	Clearly there is not evidence for this; mostly because we haven't looked and categorized those individuals as such. But inherently, I think it may make the most sense when thinking about the big picture. A continuous system with 5 bins (including the rapid metabolizer) is more amenable to harmonization across other CYPs and DMEs at large, though the current state of evidence may not support well defined phenotypes in the rapid range. I think doing this now will lead to less disruption in the future, which is why I favor this option.	12/18/2018 10:46 AM

3	The main impetus for having a rapid category is the fact that CPIC offered up that category in their 2017 article (See Table 2: Caudle et al: Genetics in Medicine 19:215-223, 2017). Even if there are only a few labs that have made this category for their interpretations, it raises questions about whether CPIC is serious when they publish things like this and it raises questions about how frequently they will make changes that impact clinical labs. For Mayo, we already had a category of EM-UM, prior to the article, so rapid was a natural transition for us. And we can easily get to a 'rapid' when there is a person who is CYP2D6*1x2/*41, for example, and there are many others. We operated off of the premise that rapid ranged from activity score of roughly >2 to 3. Another issue that I have with deleting rapid now is that it puts CYP2D6 out of synch with other CYPs, chiefly, CYP2C19. And if it is eliminated and ultrarapid starts at activity score of 2.25 or even 2.5, a CYP2C19*1/*17 will be a 'rapid' but a CYP2D6*1x2/*41 will be an ultrarapid when they have roughly the same activity score according to my read of the literature. (Activity score, we are told, has little pertinence to % of normal allele activity. But it is almost impossible not to correlate the two. My read of the literature on CYP2C19*17 is that the activity is 140-160% of a *1. Therefore, it seems natural that the activity score would be 1.4-1.6. Hence, a *1/*17 would have a composite activity score of 2.4-2.6. Is that rapid? Or is it now ultrarapid?) Parenthetically, we have published our phenotype ranges (see Ji Y et al: J of Molecular Diagnostics 18:438-445, 2016, table 2, EM to UM is now rapid). We did not explicitly give activity scores, but in the background, that was how we were thinking. Some have said that there is little literature on rapid for CYP2D6. I might not know the evidence for CYP2C19's rapid category but is there more or less evidence that this is a valid category in CYP2C19?	12/17/2018 2:41 PM

Q2 Are you in favor of using a continuous scale of activity scores for defining CYP2D6 phenotype based on genotype?

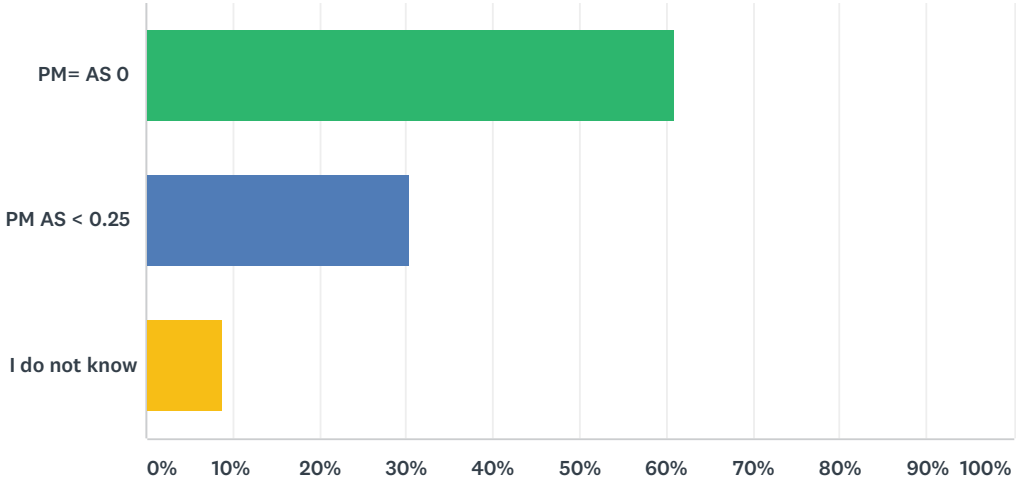
Answered: 23 Skipped: 0



ANSWER CHOICES	RESPONSES	
No	30.43%	7
Yes	69.57%	16
TOTAL		23

Q3 If we choose to add a continuous scale for defining CYP2D6 phenotype based on genotype/activity score, which do you prefer for poor metabolizer (we will decide on other phenotype (IM, NM, UM and RM (if needed)) groupings in a subsequent survey). Please provide any supporting references and rationale.

Answered: 23 Skipped: 0



ANSWER CHOICES	RESPONSES	
PM= AS 0	60.87%	14
PM AS < 0.25	30.43%	7
I do not know	8.70%	2
TOTAL		23

#	PLEASE PROVIDE SUPPORTING REFERENCES AND A RATIONALE	DATE
1	I would prefer stating not only the phenotype but also its score, to allow distinguishing a zero expression phenotype from a low activity phenotype. An alternative would be in-between categories.	1/7/2019 11:49 PM
2	This is the most clear option and is most likely to stay consitent over time	1/7/2019 10:58 AM
3	It would seem to reflect the biology most accurately: Two non-functional alleles means zero activity, i.e. = 0.	1/5/2019 11:25 AM
4	the evidence is logic. if we are not doing categorization of the activities, anything above 0 could have a number.	1/4/2019 3:41 PM
5	This category will correctly identify patients at the highest risk of drug side effects and pro-drug inefficacy.	1/4/2019 1:46 PM
6	As CYP2D6 activity data I previously sent, CYP2D6*10 should be considered as almost PM. Ref.: Functional Characterization of Wild-type and 49 CYP2D6 Allelic Variants for N-Desmethyltamoxifen 4-Hydroxylation Activity. Drug. Metab. Pharmacokinet. 28(5): 360-366(2014)	1/4/2019 4:19 AM
7	This would keep the definition of poor metabolizer as two non-functional alleles. Avoiding confusion for clinicians is important and a change of definition of the PM AS could be a problem regarding FDA label guidance, which often mentions PM.	1/3/2019 8:09 PM

8	I don't have evidence really to support this, but it seems logical based on *10 having a 0.25 AS and resulting in IM phenotype.	1/3/2019 11:50 AM
9	Currently no combination of alleles provide an activity score of less than 0.25. Thus, without knowing what alleles may fall between 0 and 0.25, it is difficult to answer. From a clinical implementation standpoint, it may be easier to convey this information using 0 as PM, >0 to 1 as having some metabolic activity (IM) and so forth.	1/3/2019 10:43 AM
10	For CYP2D6, the definition of a PM involves being positive for two absence of activity alleles and unlike some other phenotype-genotype relationships in CYP2D6 the effect seems clear and uncontroversial. I know of no CYP2D6 PM examples where there is a small amount of residual activity so the AS of 0 seems obvious.	1/3/2019 9:46 AM
11	PMs defined as < 0.25 will allow us to classify alleles with severely decreased or little function as PMs, e.g. alleles with less than 5-10% activity compared to *1 (this could be based on in vitro data).	12/27/2018 10:34 AM
12	I'm in favor of making PM=0, IM>0-0.99, NM 1-2, RM greater than 2 to 2.99, and UM equal to or greater than 3. This allows for a nice bell shaped curve and a similar binning system can be applied to other CYPs and drug metabolizing enzymes. It allows for harmonization across other enzymes.	12/18/2018 10:53 AM
13	In the absence of a category between poor and intermediate, PM may include very low activity; e.g. for tamoxifen PGx it even appears that PM/*10 activity (AS=0.25) is more closer a PM than an IM	12/18/2018 9:32 AM
14	During a quick reference search i could not find good references which investigated the differences between an AS of 0 and 0.25. In my opinion the current amount of evidence has to be reviewed whether we can objectively find a difference between the two scores and make a decision based on this evidence	12/18/2018 5:05 AM
15	A PM should be 0 as it locks in the bottom activity scale. I know it become tricky when one is dealing with a diplotype especially when using NGS and one allele has a variant with unknown activity, but we need to lock in that bottom scale.	12/17/2018 8:39 PM
16	CYP2D6 *5/*10 has more activity in vitro than CYP2D6 *4/*4 for tolterodine(Oishi et al., 2010, PMID 20530222).	12/17/2018 6:10 PM
17	There are no references for this. It just makes sense that an activity score that low is not intermediate. In this regard, I find Figure 2 of the Caudle et al: Genetics in Medicine 19:215-223, 2017 article useful in visualizing the categories.	12/17/2018 2:47 PM
18	The only known activity scores right now aside from *1 being "normal" activity, as that will set the standard, is that a no activity allele has 0 activity. Everything else is still unknown so it make the most sense to restrict this group to only two copies of non-functional alleles.	12/17/2018 1:03 PM