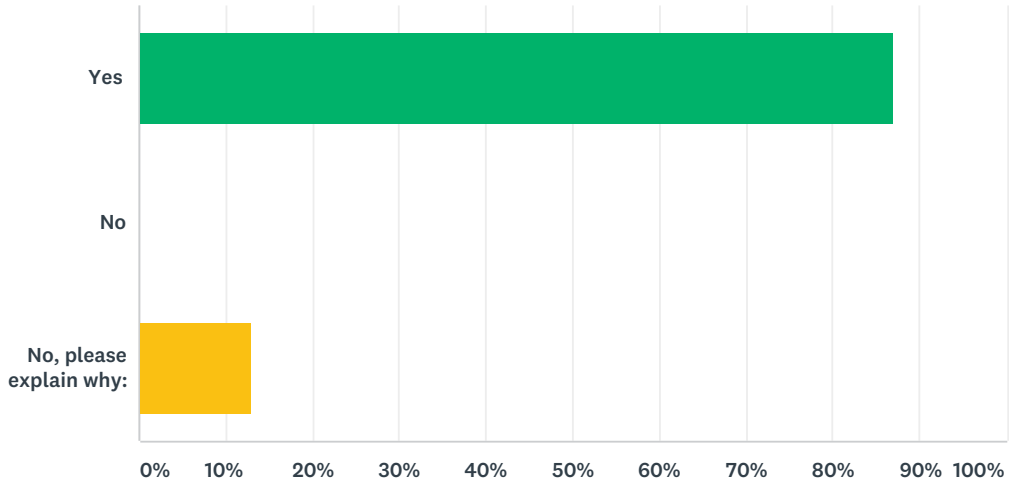
Q1 Do you agree with this recommendation to proceed with option 1?

Answered: 31 Skipped: 0

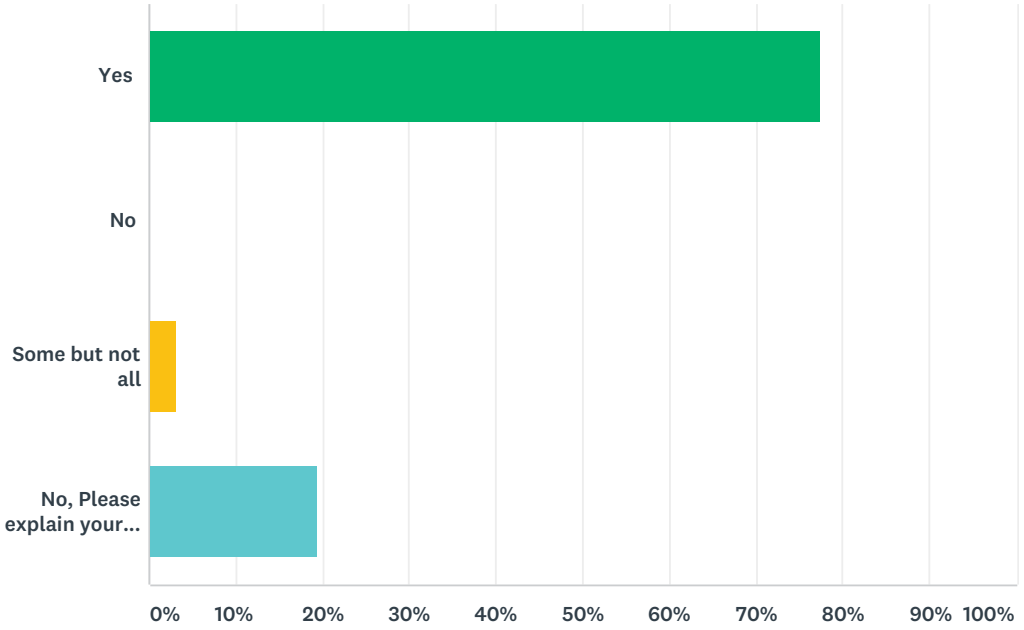


ANSWER CHOICES	RESPONSES	
Yes	87.10%	27
No	0.00%	0
No, please explain why:	12.90%	4
TOTAL		31

#	NO, PLEASE EXPLAIN WHY:	DATE
1	both options do not allow the use of an algorithm b/c of the gaps (0-0,25 and 1-1,25)	8/15/2018 4:04 PM
2	As I told previously, CYP2D6*10 has almost no enzymatic activity according to the previous reports. Hence CYP2D6*10/*10 need to be classified as poor metabolizer at least in Asian population.	8/15/2018 5:00 AM
3	I don't agree with the categorization of 1.25 as a Normal Metabolizer, i.e. that *1/*10 would be consistently considered as normal when the data is unclear for these patients depending on the medication. I would consider narrowing the "normal" range and expanding the IM range, since an additional category of phenotypes was abandoned.	8/13/2018 4:34 PM
4	We need to account for Rapid. Again, this is something that clinical labs have implemented for genes and now we are threatening to remove it creating a need to change tests. You see, clinical labs have to go to great effort to change reports and categories. It is expensive and not at all sustainable for us to change things like this. Also, there are gaps between the ranges you are showing. Eventually, if not now, allelic combinations will land in those gaps. Alleles do not have just 0, 0.25, 0.5, and 1 for an activity score.	8/3/2018 8:55 AM

Q2 Do you agree that all of these alleles containing the 100C>T should also have an activity value of 0.25?

Answered: 31 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	77.42%	24
No	0.00%	0
Some but not all	3.23%	1
No, Please explain your answer	19.35%	6
TOTAL		31

#	NO, PLEASE EXPLAIN YOUR ANSWER	DATE
1	activity scores should not be assigned democratically but should solely be based on functional data (in vitro or in vivo)	8/15/2018 4:07 PM
2	I dont think the data (in vitro) provide a clear enough picture on the relative activities of the alleles listed above. For example, the Vmax/Km ratio for *49 vs *10 varies based on the substrate utilized (PMIDs 19158312,18784265 & 4647041). I am not convinced that, while *10 and *49 are both decrease of function alleles, they have the same relative activities. Another in vitro study very recently released (Williams, I. S., Gatchie, L., Bharate, S. B. and Chaudhuri, B. (2018) Biotransformation, using recombinant CYP450-expressing baker's yeast cells, identifies a novel CYP2D6.10A122V variant which is a superior metaboliser of codeine to morphine than the wild-type enzyme. ACS Omega, 3 (8). pp. 8903-8912.) describes a novel *10 variant (containing the AA change A122V) that metabolizes codeine into morphine better than the basic *10 allele. I think it is better to wait for functional data (in vitro or in vivo, or better, both) before binning alleles solely based on a SNP (especially those that are decrease of function SNPs, like *10) that they harbour.	8/15/2018 12:27 PM
3	As I described in the answer to the question 1, 100C>T should be classified in null group. It is clear that CYP2D6*10/*10 should be classified in poor metabolizer. Classification should be established considering this fact.	8/15/2018 5:05 AM

4	Generally speaking, when curating a given allele with without phenotype data, you need to give a range of possible functions. You need to extrapolate what you know from the variants present (i.e. 100C>T AS 0.25), determine if there are other variants which impact (i.e. a truncating variant) etc. From that you might be able to derive a solid activity score (i.e. truncation leading to AS=0) but for others you cannot be precise. For example: *37 has no data that I can find. We would assign it a 0-0.25 (assuming that *10 remains a 0.25 due to the 100C>T). So, I think all of these would best fit into that range 0-0.25 because we don't know the phenotype. One exception might be *72, which in vitro has been found to have no activity. https://www.ncbi.nlm.nih.gov/pubmed/19158312. This one might be activity score of 0.	8/3/2018 10:01 AM
5	I don't think functional for the uncertain alleles is wholly dependent on the 100C>T	8/2/2018 12:20 PM
6	Definitely *10, *49, *54, and *72. Not sure about the others but would let CYP2D6 guideline authors weigh in.	8/2/2018 11:18 AM

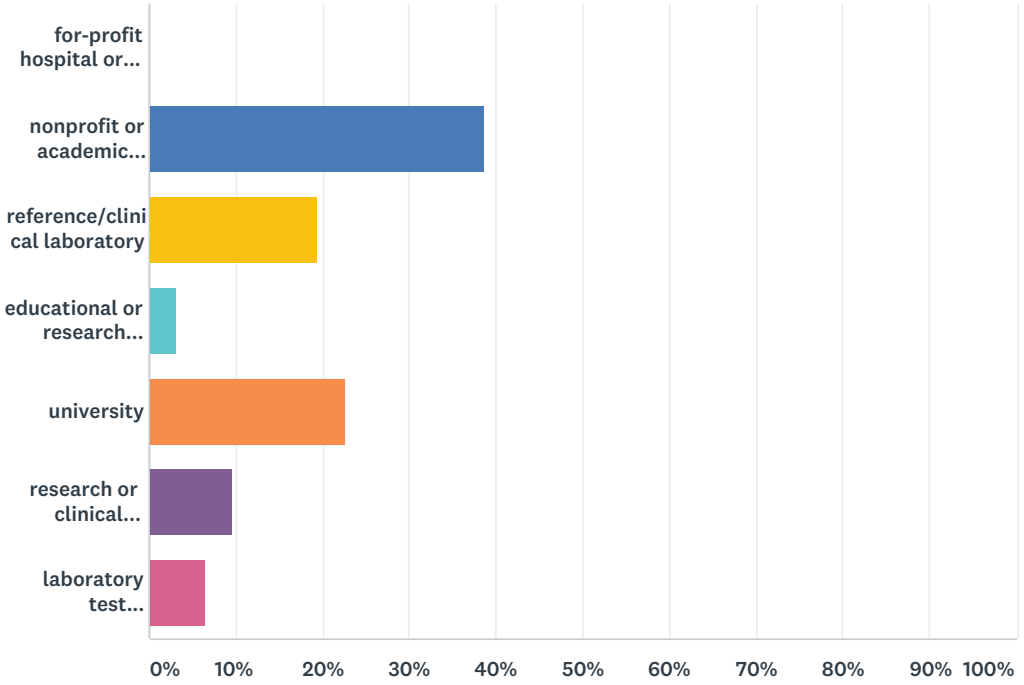
Q3 Once CPIC adopts this new CYP2D6 genotype to phenotype system, other alleles will be evaluated for downgrading to an activity value of 0.25. What other alleles do you think CPIC should evaluate further? Please provide your rationale with supporting references for your recommendation.

Answered: 14 Skipped: 17

#	RESPONSES	DATE
1	None at this moment of time.	8/16/2018 4:44 PM
2	All other common decreased function alleles such as *17, *41, *29	8/16/2018 9:44 AM
3	I do not have any suggestions.	8/16/2018 4:36 AM
4	see #2	8/15/2018 4:08 PM
5	Also remember *36 + *10 hybrid (PMID 22004686). CPIC should evaluate the classification of *41 further. In some studies e.g. PMID 20881950 and 20588073 the effect of the *41 on the phenotype on seems greater than other alleles with reduced function	8/15/2018 1:53 PM
6	None that come to mind at this time.	8/15/2018 12:28 PM
7	*41 (Wickramage 2017)	8/13/2018 4:51 PM
8	Still controversy about scoring *2a and *35 for gain of function. Consider for our next evaluation	8/8/2018 2:45 PM
9	Thinking more broadly. There are alleles which should have their activity scores defined more. *2 and *2A-tamoxifen data suggests that *2 is not = to *1. This would impact any other allele with 2850 variant similar to 100C>T impacting alleles containing that variant. *53 may have increased activity. see http://dmd.aspetjournals.org/content/dmd/36/12/2460.full.pdf *60 is truncating and listed as 'unknown' but it should be null. *70 should function at least like a *29 (reduced). *81 has another stop and should be null. *96 has another stop but is later in the gene... I know this is beyond what you were asking for but it would be nice to refine many alleles.	8/3/2018 11:01 AM
10	*17 needs evaluation as it's relatively common in Africa	8/2/2018 12:23 PM
11	2C9	8/2/2018 12:21 PM
12	All the 100C>T containing variants and maybe others.	8/2/2018 11:19 AM
13	I would need much more time to evaluate them all, and I currently cannot do that. Apologies.	7/31/2018 9:06 PM
14	have not considered this yet	7/30/2018 4:01 PM

Q4 Which of the following describes your workplace setting?

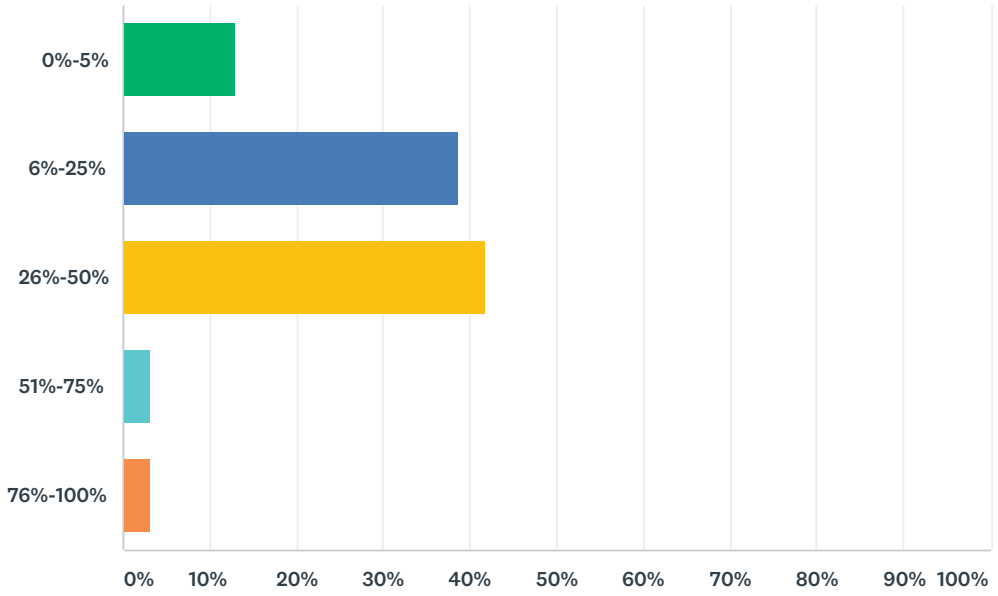
Answered: 31 Skipped: 0



ANSWER CHOICES	RESPONSES	
for-profit hospital or clinic	0.00%	0
nonprofit or academic hospital or clinic	38.71%	12
reference/clinical laboratory	19.35%	6
educational or research resource	3.23%	1
university	22.58%	7
research or clinical institute	9.68%	3
laboratory test interpretation service	6.45%	2
TOTAL		31

Q5 What percent of your time is related to work involving CYP2D6?

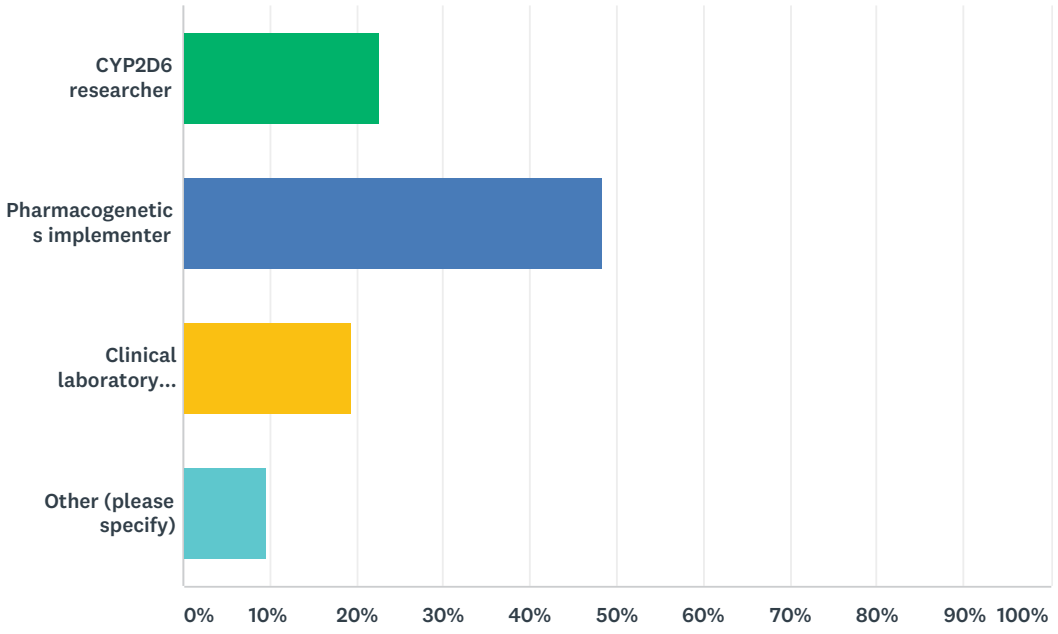
Answered: 31 Skipped: 0



ANSWER CHOICES	RESPONSES	
0%-5%	12.90%	4
6%-25%	38.71%	12
26%-50%	41.94%	13
51%-75%	3.23%	1
76%-100%	3.23%	1
TOTAL		31

Q6 Which of the following best describes your primary job?

Answered: 31 Skipped: 0



ANSWER CHOICES	RESPONSES	
CYP2D6 researcher	22.58%	7
Pharmacogenetics implementer	48.39%	15
Clinical laboratory professional	19.35%	6
Other (please specify)	9.68%	3
TOTAL		31

#	OTHER (PLEASE SPECIFY)	DATE
1	PGx researcher	8/15/2018 5:34 PM
2	PGx Research	8/9/2018 1:16 PM
3	Professor	8/2/2018 12:24 PM