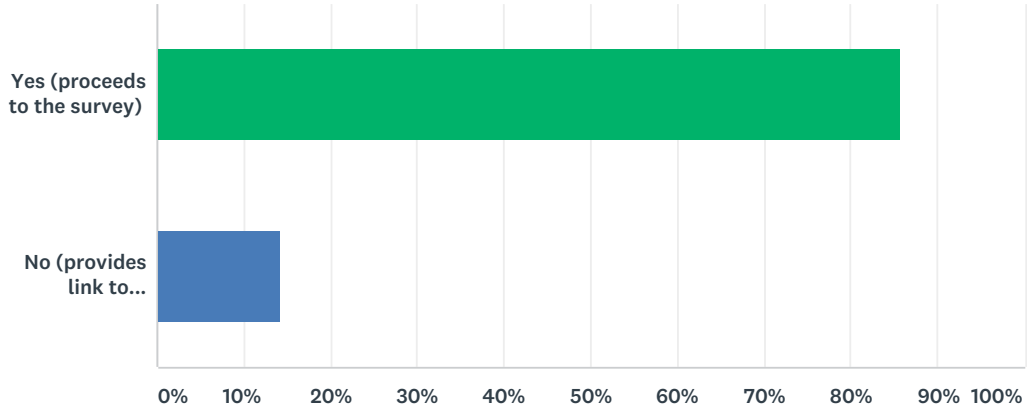
Q1 Did you either call in to this discussion on August 1st OR listen to the recorded discussion?

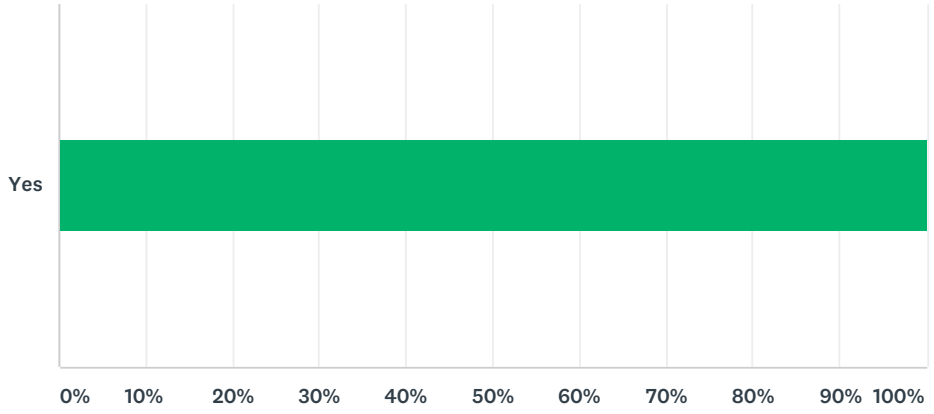
Answered: 35 Skipped: 1



ANSWER CHOICES	RESPONSES	
Yes (proceeds to the survey)	85.71%	30
No (provides link to webinar)	14.29%	5
TOTAL		35

Q2 I have watched the webinar and I am ready to continue with the survey.

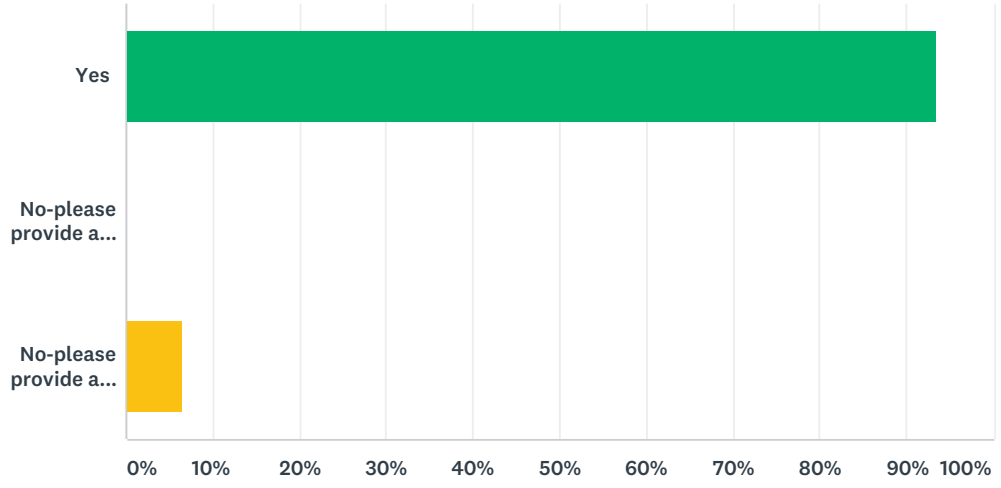
Answered: 3 Skipped: 33



ANSWER CHOICES	RESPONSES	
Yes	100.00%	3
TOTAL		3

Q3 Do you agree with this recommendation to proceed with the use of the activity scores, the possibility of downgrading some alleles to a new functional group (AS = 0.25; severely decreased function-assuming we have convincing data) and categorizing AS = 1 as intermediate metabolizers AND/OR creating a new phenotype group between IM and PM?

Answered: 31 Skipped: 5



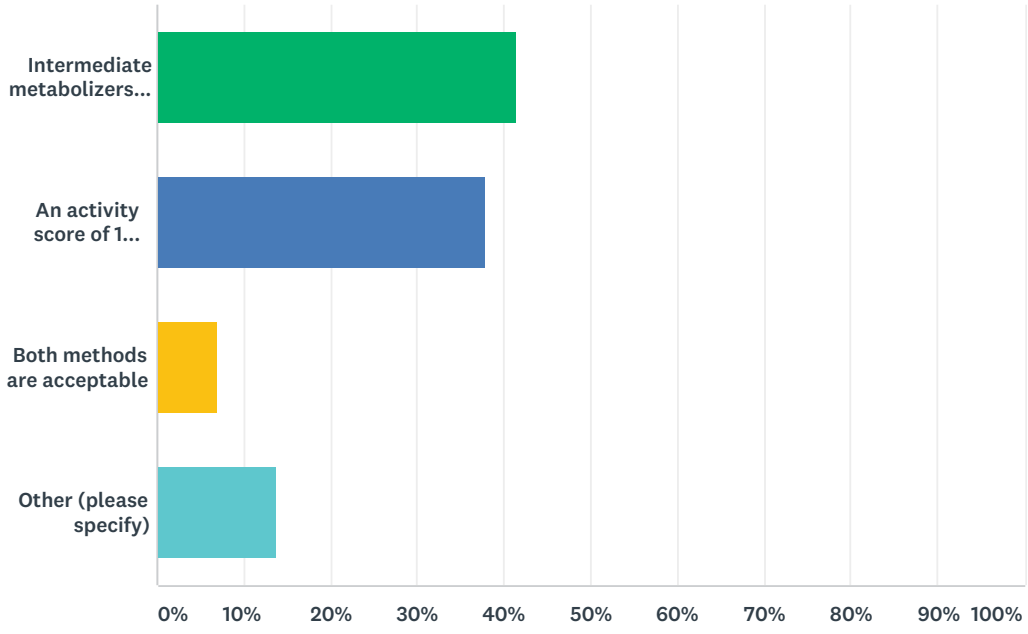
ANSWER CHOICES	RESPONSES	
Yes	93.55%	29
No-please provide a comprehensive list of references that can be used to assign percentage activity to the majority of CYP2D6 alleles of known function. See https://api.pharmgkb.org/v1/download/file/attachment/CYP2D6_allele_functionality_reference.xlsx for a list of alleles with known function. The suggested calculation for a percentage activity (PA) system for decreased function alleles is: PA=100*((X-PM)/(EM-PM)), (see August 1st slides).	0.00%	0
No-please provide a comprehensive list of references that can be used to assign percentage activity to the majority of CYP2D6 alleles of known function. See https://api.pharmgkb.org/v1/download/file/attachment/CYP2D6_allele_functionality_reference.xlsx for a list of alleles with known function. The suggested calculation for a percentage activity (PA) system for decreased function alleles is: PA=100*((X-PM)/(EM-PM)), (see August 1st slides).	6.45%	2
TOTAL		31

#	NO-PLEASE PROVIDE A COMPREHENSIVE LIST OF REFERENCES THAT CAN BE USED TO ASSIGN PERCENTAGE ACTIVITY TO THE MAJORITY OF CYP2D6 ALLELES OF KNOWN FUNCTION. SEE HTTPS://API.PHARMGKB.ORG/V1/DOWNLOAD/FILE/ATTACHMENT/CYP2D6_ALLELE_FUNCTIONALITY_REFERENCE.XLSX FOR A LIST OF ALLELES WITH KNOWN FUNCTION. THE SUGGESTED CALCULATION FOR A PERCENTAGE ACTIVITY (PA) SYSTEM FOR DECREASED FUNCTION ALLELES IS: PA=100*((X-PM)/(EM-PM)), (SEE AUGUST 1ST SLIDES).	DATE
1	I am in favor of a "mixed" system, i.e. for alleles where enough data exist, to establish an activity score based on the demonstrated activity of the protein, in a substrate-specific manner. For alleles (and/or substrates) with insufficient literature, the functional score would be 0, 0.25, 0.5, 1 etc. Phenotypes would be then called "poor to intermediate", "intermediate to normal" etc.	10/17/2017 9:49 AM

2	I believe 0.25 intervals is overreach, particularly when function will be substrate dependent.	10/11/2017 3:33 PM

Q4 Assuming that we do NOT downgrade any alleles to receive a value of 0.25 for activity calculation, which method would you prefer for assignment of CYP2D6 phenotype for an activity score of 1?

Answered: 29 Skipped: 7



ANSWER CHOICES	RESPONSES	
Intermediate metabolizers would be defined as Activity Score of 0.5 to 1.UM: AS>2NM: AS=1.5 to 2IM: AS 0.5 to 1 PM: AS = 0	41.38%	12
An activity score of 1 would be categorized in its own phenotype group. Terminology to be determined.UM: AS>2NM: AS=1.5 to 2New phenotype group: AS= 1 New phenotype group AS=0.5PM: AS = 0	37.93%	11
Both methods are acceptable	6.90%	2
Other (please specify)	13.79%	4
TOTAL		29

#	OTHER (PLEASE SPECIFY)	DATE
1	Of the above choices, I lean to the first, but continuing discussion is important. To leave a comment here, I had to choose "Other". As we know, the reality is wide variability in activity even within specific genotypes (Gaedigk 2013, Fig 1). It would be helpful to compare this type of data between individuals with two reduced function alleles versus one normal allele and a nonfunctional allele. They both have an activity score of 1, but how much do these two groups differ from each other? In a phenotyping system from a previous testing kit, two reduced function alleles were categorized as IM and a normal plus nonfunctional allele were categorized as EM. Compiling of all data for each combination of alleles and each drug with known information for CYP2D6 activity and drug response in patients would be very helpful to see what is known and where the gaps are before we make a decision, since we want any decision to be based on clinical usefulness.	10/27/2017 5:32 PM
2	GAS <0,5 PM GAS 0,5 + 1 IM GAS 1,5 - 2,5 EM GAS > 2,5 UM	10/20/2017 1:05 PM

3	I would introduce the notion of rapid metabolizer with CYP2D6. For example, *1/*9x3 is likely not as rapid as *1xN/*1xN. As we work with investigators who are able to determine the duplication number in large study groups, we need to be able to propose an interpretation for every possible genotype/phenotype. A reasonable option would then be: UM: AS>2.5 RM: AS>2 to 2.5 NM: AS=1.5 to 2 IM: AS 0.5 to 1 SM (Slow): 0 to 0.5 PM: AS = 0	10/17/2017 10:00 AM
4	I don't believe that you can get by without downgrading some alleles so I prefer the model shown here. UM: 3 and over Rapid: over 2.25 to less than 3 Normal: 1.75 to 2.25 Intermediate to normal: over 1.25 to less than 1.75 Intermediate: 0.75 to 1.25 Poor to intermediate: 0.25 to less than 0.75 Poor 0 to less than 0.25 I am surprised that none of the models you present have rapid in them. And UM is anything over 2. I did not think something like this was under consideration. I might be missing the point...	10/4/2017 3:49 PM

Q5 Please explain your answer to the previous question (please reference available literature).

Answered: 27 Skipped: 9

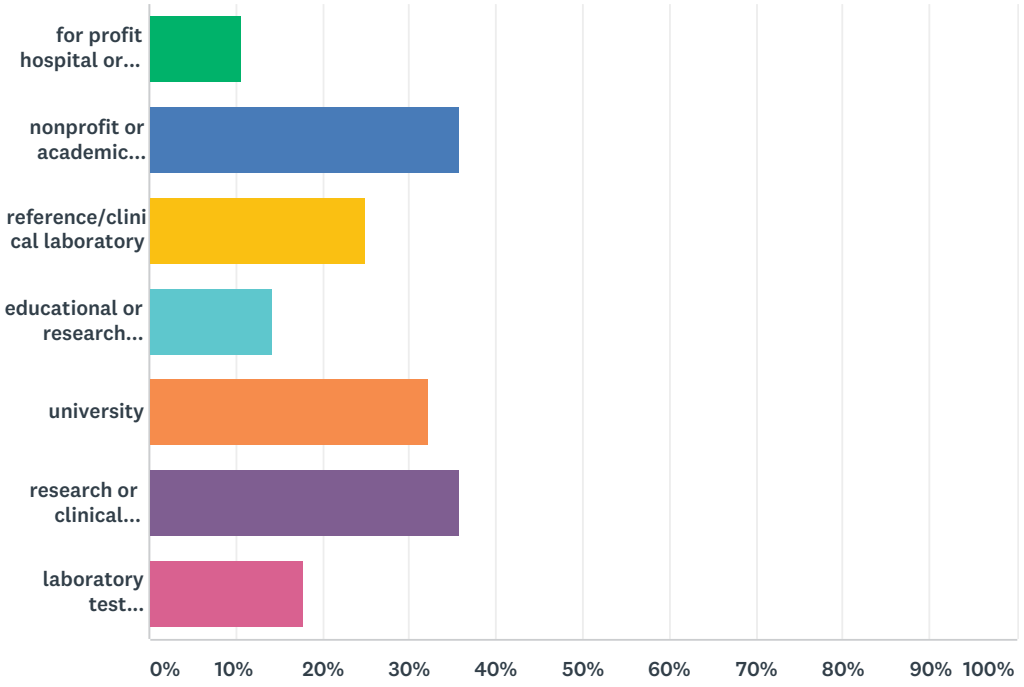
#	RESPONSES	DATE
1	I added a note about this in the comments section of question 3. Which of the two approaches is better would be best determined from the clinical evidence from studies of patient response with specific drugs, not just from enzyme activity research.	10/27/2017 5:39 PM
2	1) For several drugs a clinically relevant effect on PK has been observed in patients with one functionale allele compared to patients with two functional alleles. 2) At this time for most drugs dosage recommendations will not be very different for those with AS 0.5 and 1.	10/24/2017 8:25 AM
3	It is not realistic to make such differences	10/23/2017 2:55 AM
4	After extensive discussion the consensus in the DPWG group is that for practical reasons we would like to keep the CYP2D6 classification as it is currently implemented: GAS <0,5 PM GAS 0,5 + 1 IM GAS 1,5 - 2,5 EM GAS > 2,5 UM With regard of to a new functional group (AS = 0.25; severely decreased function) the group feels that adding an additional group to the system adds complexity while improvement for individual dose prediction is probably limited. In addition it was suggested that substrate specificity probably has the largest impact on alleles with a score between 0-1. Of course if convincing data are available we are happy to reconsider.	10/20/2017 1:06 PM
5	This score is the consensus score of the DPWG. GAS 1 is considered IM, also to identify these patients who are more likely to experience pehnoconversion when co-treated with a CYP2D6 inhibitor	10/20/2017 9:16 AM
6	I have no references - I like the idea of the AS= 1 being a IM, because this is where I struggle when writing reports. While anecdotal, I have had some patients (*1/*4) that get called normal metabolizers that have had inadequate pain relief on opiods. Of course they may have a rare mutation/variant not detected on my assay and they are perhaps poor metabolizers. The biggest issue is the inconsistencies between CPIC and DPWG. In general, for most of the other CYP genes (exception is CYP2D6), when you have *1/non-functional allele = intermediate metabolizer. It would be good to have harmonization.	10/19/2017 9:40 AM
7	I think the first option is preferable, because creating a new "phenotype" category will disrupt current implementation strategies. I also think that this many metabolizer groupings will be unlikely to be supported by adequate data for the vast majority of drugs.	10/19/2017 9:11 AM
8	The inclusion of the additional AS would allow for a more precise estimate of the CYP2D6 activity at the lower end. This would also allow for more precise dosing recommendations for some important gene-drug pairs where CYPD26 is the primary Phase-I enzyme (e.g., for TCAs or tamoxifen)	10/18/2017 11:49 PM
9	Sometimes AS=1 has NM, sometimes it doesn't so it deserves its own group.	10/18/2017 2:17 PM
10	I think it is clearer to establish it's own group. I think that moves 1 from Normal to Intermediate metabolizer. That creates more issues. I think this is a substrate issue dependency and therefore needs it own group. (Literature has already been collected -- sorry Kelly)	10/18/2017 2:17 PM
11	based on literature date (e.g. tamoxifen PK-CYP2D6 [Schroth et al. Front Pharmacol 2017] and other examples) a more specified activity scoring is requested with consequences on dosing alogrithms	10/18/2017 10:59 AM

12	I believe option 1 is the best choice based on the information that is currently available. Regarding the 2nd option in question #4, I am not sure how helpful it would be to have new phenotype groups, as long as that it is carefully stated that the actual phenotype of samples categorized into any of the predicted metabolizing groups can differ (ie, it is possible for a sample placed in the NM group to actually be a UM, IM or PM). As I write that sentence, I feel a bit disappointed that this is really the case, but, we must accept that the literature is not sufficiently extensive (low "n's" for certain genotypes) nor accurate (a certain percentage of the genotypes assigned to samples that were phenotyped are simply not correct). I apologize that I cannot provide references for this. However, I say this because my group has allele-specific sequenced (Sanger) upwards of 1000 CYP2D6 alleles, and have found that ~25-30% of them are novel (this data is unpublished).	10/18/2017 10:35 AM
13	CYP2D6 * 10 is a high frequency in Asian populations. Therefore, the activity score of CYP2D6 * 10 is very important in Asians. Generally, the CYP2D6*10/*10 carrier has been considered as normal metabolizer (NM) because of the CYP2D6*10 allele's activity score. However, the metabolic ratio of CYP2D6*10/*10 genotype is hard to consider as same as CYP2D6*1/*5's, even their activity scores are same(Lee et al.,Drug Metab Dispos. 2009 Jul;37(7):1464-70). In the color visualization and silhouette value using the k-means cluster analysis, the CYP2D6*10B/*10B was also classified with the same cluster what generally known as intermediate metabolizer (IM), not with CYP2D6*1/*1's cluster(Kim et al., TCP 2017. 25(3):147-152). If the activity score of CYP2D6*10 considers as 0.5, then it doesn't make sense; it's below 0.5. Therefore, it is more reasonable that the activity score of CYP2D6*10 allele is 0.25, otherwise at least, it should be lower than 0.5.	10/17/2017 8:05 PM
14	The methodology of incorporating new phenotype groups would account for different case scenarios. It would offer a better approximation of the patient's activity status and allow the pharmacist or physician to make a better informed decision. I.e. a "poor" metabolizer (no CYP2D6 activity whatsoever) should be distinguished from a "slow" (residual activity; may be significant depending on context, for example in pregnancy when CYP2D6 activity increases when at least some functional protein exists). In absence of large-scale clinical studies, providing the most accurate information available to the clinician is a better option, even if it implies that providers will need greater training (increasingly available in universities and colleges).	10/17/2017 10:08 AM
15	Having a separate phenotype classification for AS=1 would account for the substrate dependency and will help disambiguate between AS of 1.5 or 2 (NM) and AS 0.5 (IM) and those with AS of 1 which depending of the substrate can result in a normal clearance or decreased clearance.	10/16/2017 5:11 PM
16	Assuming that *10 is not downgraded, then data on *10/*10 (AS=1) indicates significant reduction in enzyme function compared to AS=2. (Hicks et al., 2014, Curr Drug Metabolism, 15, 218-232). This supports IM assignment for AS=1.	10/16/2017 11:42 AM
17	The system with an group for an AS of 0.5 and AS of 1 allows for more granular therapeutic recommendations for gene-drug interactions when there is evidence for a distinct difference between an AS of 0.5 and AS of 1 (for instance CYP2D6-atomoxetine, PMid 26660002) while in the case there is no clear difference between an AS of 0.5 and 1 the same therapeutic recommendation can be provided for both groups.	10/15/2017 6:59 AM
18	I am okay with both options. My interest is enabling diplotypes with an AS of 1 to be separate from NMs, as being heterozygous for one functional allele and one no function should be distinct from two functional allele patients...either IMs or through two newly defined classifications.	10/14/2017 7:15 PM
19	The clinical outcome after tamoxifen therapy and plasma endoxifen level are almost similar between *10/*10 (or *10/PM) and PM/PM. Hence, *10/*10 and *10/PM should be categorized in same group as PM/PMs.	10/14/2017 3:11 AM
20	AS=1 an intermediate because an individual with two functional alleles will then have AS=2	10/12/2017 2:13 AM
21	My answer (to define an IM based on AS of 0.5-1) is based on simplicity of terminology and my perceived safety to the patient. Adding a new category of phenotype will require new dosing guidelines and education, and I don't believe the precision for guiding dosing with an IM is mature enough for most clinicians as it is. Also, as CAP PT performance has shown, there is currently inconsistency among whether laboratories classify an AS of 1 as an IM or a NM; this is a big reason that the CAP is not yet grading phenotype assignment performance. The other reason for my response is based on the increased likelihood for DDIs in patients with an AS of 1, which may not be clinically appreciated if that phenotype is called "normal." I think that the consequences of assigning an IM phenotype for an AS of 1 would improve awareness of a person's susceptibility to DDIs and would instill caution in prescribing CYP2D6 substrates. This concern of safety intensifies when DMEs coded by multiple potentially variant genes are involved in drug metabolism (e.g. PMID: 27198207).	10/11/2017 4:27 PM

22	In the absence of an extensive database assessing the function of each allele against a library of drug substrates, any gene dosage assignment will be approximate. There is no sufficient data to get into finer gradations of function.	10/11/2017 3:33 PM
23	While I would support the 1st option, I actually would prefer to see the NM group have a slightly larger range. 1.5-2.5, perhaps? I think it represents a more realistic distribution of the middle of the bell shaped curve. But this will be predicated on a change of some of the scores allowing us to stay within that range. Evidence: PMID: 7616439 PMID: 27388693	10/9/2017 4:31 PM
24	AS of 0.5, 1 and >1 are sufficiently different for many drugs based on the examples shown in the calls. This more granular system better reflects the wide range of activity.	10/5/2017 11:34 AM
25	I view AS as a temporary system to be replaced by PA. Therefore, I am content with whichever modifications to AS are necessary to reconcile the existing systems.	10/5/2017 9:16 AM
26	This is the method we have used from the beginning in this lab. The method is described in essence in Ji Y et al: Journal of Molecular Diagnostics 18: 438-445, 2016	10/4/2017 3:53 PM
27	In the case of tamoxifen, and AS of 0.5 corresponding to a *5/*10 represents a severe decrease in activity and calling this phenotype group "intermediate" is incorrect	10/4/2017 2:58 PM

Q6 Which of the following describes your workplace setting (choose all that apply)?

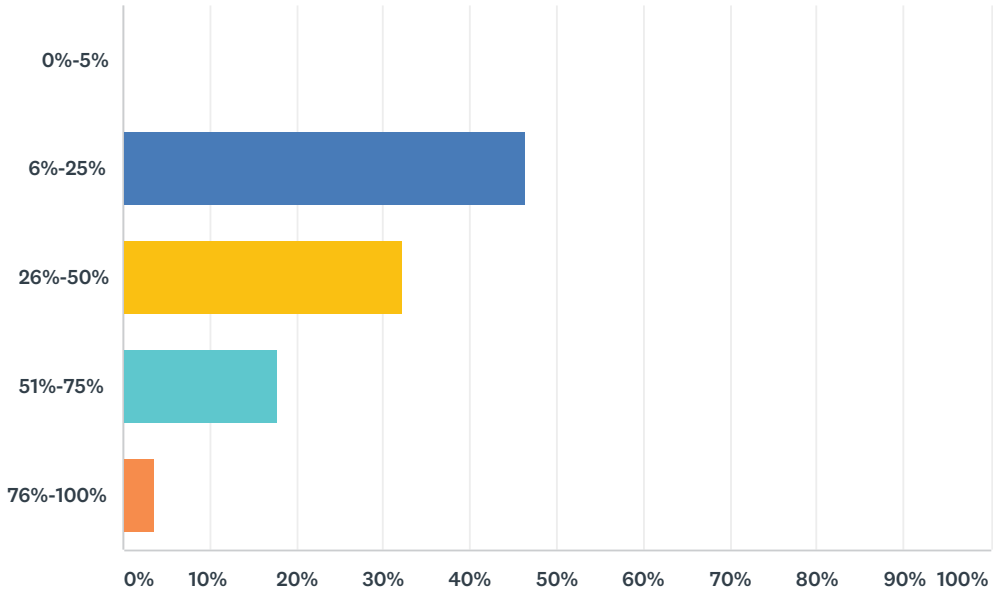
Answered: 28 Skipped: 8



ANSWER CHOICES	RESPONSES	
for profit hospital or clinic	10.71%	3
nonprofit or academic hospital or clinic	35.71%	10
reference/clinical laboratory	25.00%	7
educational or research resource	14.29%	4
university	32.14%	9
research or clinical institute	35.71%	10
laboratory test interpretation service	17.86%	5
Total Respondents: 28		

Q7 What percent of you time is related to work involving CYP2D6?

Answered: 28 Skipped: 8



ANSWER CHOICES	RESPONSES	
0%-5%	0.00%	0
6%-25%	46.43%	13
26%-50%	32.14%	9
51%-75%	17.86%	5
76%-100%	3.57%	1
TOTAL		28