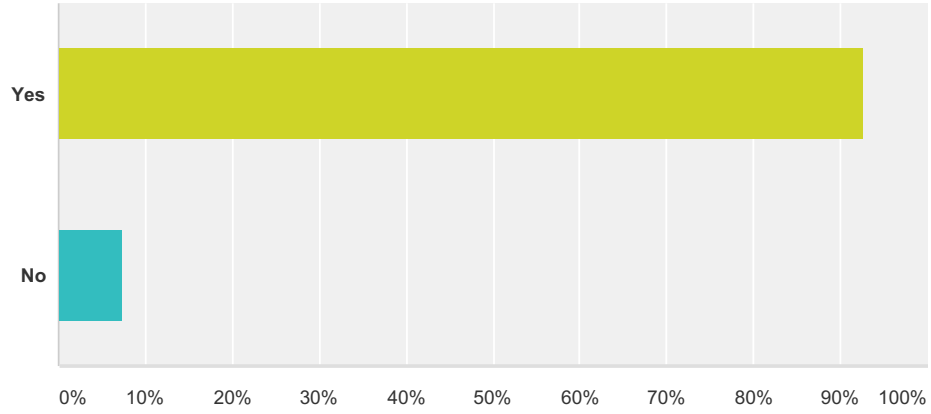
Q1 Based on the current evidence (see attached spreadsheet and any additional studies you may be aware of), do you think there is a clinically significant difference between a CYP2D6 activity score of 1 and 2?

Answered: 27 Skipped: 0



Answer Choices	Responses	
Yes	**92.59%**	25
No	**7.41%**	2
Total		**27**

#	Please explain and provide references and examples that support your opinion.	Date
1	but it depends on the drug. For TCAs, where there is a fairly narrow therapeutic index, I believe Julia Stingl's article predicted a reduced dose for some of those drugs if they had only one functional allele. Also, with the current AS classification, a *10/*10 would be and AS of 1, and there are clearly differences with Asian *10/*10's compared to AS of 2.	5/12/2017 9:17 AM
2	based on our longstanding expertise, there is a drug specific difference between activity score 1 and 2. Particulary, the Tamoxifen-example clearly shows that score 1-patients do have significantly reduced endoxifen-levels compared to score 2. Moreover, based on our extensive work on 2D6 activity/protein levels in human liver compared to 2D6-genotypes it is absolutely clear that protein expression as well as functional activity is significantly reduced in score 1 individuals.	5/4/2017 1:18 AM
3	Based on the current evidence in the provided spreadsheet in my opinion there is indeed a clinically significant difference between cyp2d6 activity score of 1 and 2. However, this effect is most frequently seen in the arms that compare *10/*10 vs. the *1/*1 genotype and most frequently in certain drugs (atomoxetine (PMID 26254792 & 17610534), citalopram (23981149), codein (24077935), metoprolol (18834373, 12915955 and 10223777)). This effect might not be relevant for all drugs.	5/2/2017 2:19 AM
4	This may be the case if another probe substrate other than dextromethorphan is used to correlate genotype and phenotype. PK/PD studies with drugs like pimozide should be examined carefully, especially is Asians where individuals with AS=1 (such as those with genotype: *10/*10 are common). Examination of PK studies in different genotype groups with another sensitive CYP2D6 substrate such as desipramine may help quantify the change between individuals with AS of 1 vs AS of 2.	5/1/2017 11:27 AM

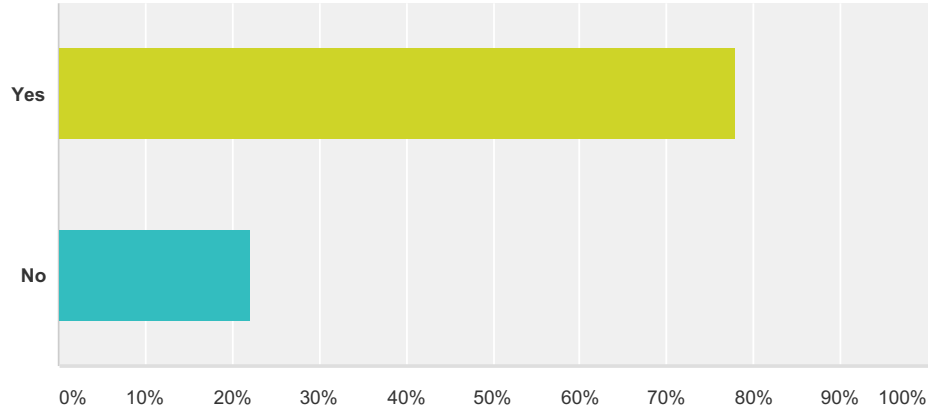
5	Ruaño G, Szarek B, Villagra D, Gorowski K, Kocherla M, Seip RL, Goethe JW, Schwartz HI. Length of Psychiatric Hospitalization Correlated with CYP2D6 Functional Status in Inpatients with Major Depressive Disorder. Biomarkers in Medicine, 7 (3): 429-439, 2013 Villagra D, Goethe J, Schwartz HI, Szarek B, Kocherla M, Gorowski K, Windemuth A, Ruaño G. Novel Drug Metabolism Indices for Pharmacogenetic Functional Status Based on Combinatory Genotyping of CYP2C9, CYP2C19 and CYP2D6 Genes. Biomarkers in Medicine, 5 (4): 427-438, 2011 Ruaño G, Villagra D, Szarek B, Windemuth A, Kocherla M, Gorowski K, Berrezueta C, Schwartz HI, Goethe J. Physiogenomic Analysis of CYP450 Drug Metabolism Correlates Dyslipidemia with Pharmacogenetic Functional Status in Psychiatric Patients. Biomarkers in Medicine, 5 (4): 439-449, 2011 Functional Phenotype: deficient	4/30/2017 11:12 PM
6	The excel sheet with a summary of studies shows that for a substantial number of substrates the pharmacokinetics differ between those with an activity score of 1 vs 2.	4/28/2017 8:50 AM
7	activity score of 2 is the ultrarapid metabolizers. I think that there is good agreement between CPIC and DPWG.	4/24/2017 6:43 AM
8	Juts looking at the spreadsheet, the differences between 1 and 2 are too small to make clinically significant differences; especially given that for most metabolic pathways other CYPs are involved (albeit minor players) and that especially the antidepressants have therapeutic indices that make a difference in AS between 1 and 2 not relevant.	4/21/2017 10:21 AM
9	There is evidence that distinguishing between score 1 and 2 is clinically relevant at least in substrates such as tamoxifen (1–4), risperidone and aripiprazole (5–7), carvedilol (8,9), codeine (10,11) and dextromethorphan (12,13). Although distinguishing a score 1 phenotype (IMs) from a score 2 phenotype (NMs) may not be clinically relevant across all substrates, we recommend keeping a classification of phenotypes as detailed as possible, specifically separating phenotypes with a score of 1 (IMs) from a score of 2 (NMs), and score 0 (PMs) from score 0.5 (“slow” metabolizers, reduced function + no function allele) for describing genotype-predicted phenotypes. This is important moving forward to report results in studies aiming at evaluating the clinical impact of genotypes on the response to different medications, and avoid discrepancies between studies on how NMs and IMs are pooled in the literature. We recognize that the typical small number of subjects per each phenotype categories may cause difficulty in interpretations of the results, but as the impact of genes on medication response is increasingly acknowledged by the industry it is reasonable to expect that larger studies will be conducted in the future; and in any case the standardization in multiple categories will allow a better, more accurate interpretation of the results. To address the substrate-specificity that seems to characterize some “reduced” and even “no function” alleles for CYP2D614 (and likely other alleles of other genes), phenotype-specific, or genotype-specific recommendations for medications can ultimately be similar between IMs and NMs; but the “pooling” of these two groups render confusing or impossible the ability to provide distinct recommendations when they exist. 1. Hertz, D. et al. In vivo assessment of the metabolic activity of CYP2D6 diplotypes and alleles. British Journal of Clinical Pharmacology 80, 1122–1130 (2015). 2. Lim, H.-S. et al. Clinical Implications of CYP2D6 Genotypes Predictive of Tamoxifen Pharmacokinetics in Metastatic Breast Cancer. J Clin Oncol 25, 3837–3845 (2007). 3. Kiyotani, K. et al. Dose-adjustment study of tamoxifen based on CYP2D6 genotypes in Japanese breast cancer patients. Breast Cancer Res Tr 131, 137–145 (2012). 4. Panomvana, D., Areepium, Rungwanonchai, Voravud & Satthaporn, S. Effects of CYP2D6 and UGT2B7 polymorphisms on pharmacokinetics of tamoxifen in Thai breast cancer patients. Breast Cancer Targets Ther Volume 5, 73–78 (2013). 5. Hendset, M., Molden, E., Knape, M. & Hermann, M. Serum Concentrations of Risperidone and Aripiprazole in Subgroups Encoding CYP2D6 Intermediate Metabolizer Phenotype. Ther Drug Monit 36, 80 (2014). 6. Novalbos, J. et al. Effects of CYP2D6 Genotype on the Pharmacokinetics, Pharmacodynamics, and Safety of Risperidone in Healthy Volunteers. J Clin Psychopharm 30, 504 (2010). 7. Van der Weide, K. & van der Weide, J. The Influence of the CYP3A4*22 Polymorphism and CYP2D6 Polymorphisms on Serum Concentrations of Aripiprazole, Haloperidol, Pimozide, and Risperidone in Psychiatric Patients. J Clin Psychopharm 35, 228 (2015). 8. Sehrt, D., Meineke, I., Tzvetkov, M., Gültepe, S. & Brockmöller, J. Carvedilol pharmacokinetics and pharmacodynamics in relation to CYP2D6 and ADRB pharmacogenetics. Pharmacogenomics 12, 783–795 (2011). 9. Honda, M. et al. Effect of CYP2D6*10 on the Pharmacokinetics of R- and S-Carvedilol in Healthy Japanese Volunteers. Biological Pharm Bulletin 28, 1476–1479 (2005). 10. Tseng, C., Wang, S., Lai, M., Lai, M. & Huang, J. Formation of morphine from codeine in Chinese subjects of different CYP2D6 genotypes. Clin Pharmacol Ther 60, 177–182 (1996). 11. Wu, X., Yuan, L., Zuo, J., Lv, J. & Guo, T. The impact of CYP2D6 polymorphisms on the pharmacokinetics of codeine and its metabolites in Mongolian Chinese subjects. Eur J Clin Pharmacol (2013). doi:10.1007/s00228-013-1573-x 12. Tateishi, T. et al. Analysis of the CYP2D6 gene in relation to dextromethorphan O-demethylation capacity in a Japanese population. Clin Pharmacol Ther 65, 570–575 (1999). 13. Sosa-Macías, Dorado, Alanis-Bañuelos, R. E., Llerena & Lares-Asseff. Influence of CYP2D6 Deletion, Multiplication, –1584C→G, 31G→A and 2988G→A Gene Polymorphisms on Dextromethorphan Metabolism among Mexican Tepehuanos and Mestizos. Pharmacology 86, 30–36 (2010). 14. Muroi, Y. et al. Functional characterization of wild-type and 49 CYP2D6 allelic variants for N-desmethyltamoxifen 4-hydroxylation activity. Drug Metab Pharmacok 29, 360–6 (2014).	4/20/2017 10:02 AM
10	There is a clinically significant difference in PK though it appears to be substrate specific. If this translates into meaningful differences in outcomes of therapy also greatly depends on the substrate of interest. In addition, AS 1 may be much more prone for interactions with CYP2D6 inhibitor and therefor you may want to separate them from the AS 2	4/20/2017 8:04 AM
11	Yes, Yoon 2000 paired with Huang, 1999, Taguchi 2003, and others. I think the literature is clear on this point. Investigators that haven't found a difference are due to low sample size.	4/19/2017 6:42 AM

12	That those heterozygous for CYP2D6 inactivating alleles show a lower activity compared with those homozygous for two "wild-type" alleles has been known since the earliest studies on phenotype-genotype relationships (see e.g. Daly AK, Armstrong M, Monkman SC, Idle ME, Idle JR. Genetic and metabolic criteria for the assignment of debrisoquine 4-hydroxylation (cytochrome P4502D6) phenotypes. Pharmacogenetics. 1991 Oct;1(1):33-41. PubMed PMID: 1688241). While I consider that there is a statistically significant difference between "activity scores 1 and 2 when comparing those homozygous for wild-type alleles with those heterozygous for an inactivating allele", it is not at all clear that this is of any clinical importance because the differences both in the original study and the supplied references are small. However, if CYP2D6*10/10 is also considered as having a score of 1 (incorrectly in my view), it is clear to me from my own experience plus the majority of references supplied concerned with *10 that those homozygous for this allele are different in terms of pharmacokinetics to wild-type individuals and a different dose or a different drug may need to be considered.	4/18/2017 1:28 AM
13	For some reduced function alleles including *10 activity differs significantly (examples shown in call). Whether this is clinically relevant likely depends on the drug.	4/18/2017 1:22 AM
14	Currently used CPIC 2D6 activity scoring is not refined and cannot be applied to all 2D6 susbtrates, particularly in regards to IM diplotypes and such diplotype groups cover a wide range of activity. The clearance attributable to an individual CYP2D6*1 copy was 2.5-fold higher as compared with CYP2D6*2 (https://www.ncbi.nlm.nih.gov/pubmed/20881950) https://www.ncbi.nlm.nih.gov/pubmed/?term=26947514	4/17/2017 8:38 AM
15	There is vast clinical evidence that AS1 is not equal to AS2 and it is impossible to list all of the literature that proves this here. Some of the evidence is found in the articles on the spreadsheet but CYP2D6 has been the subject of thousands of research publications and, on balance, the impact of an AS1 vs. AS2 is commonly found for multiple but not all substrates. I encourage this workgroup to consider the following: 1. Biological systems are on a continuum. They are rarely binary and they are difficult to lump into discrete categories. They are best described with a range of activities. From a practical perspective (i.e. in a research/clinical setting) this is difficult to deal with ranges. Researchers need huge and unobtainable numbers to test every possible phenotype when there are seven phenotype bins, for example, so it this research does not happen. It is much easier to test 3 or 4 bins because they can have the power to do that with the N they can obtain. When CPIC generates a look up table to help clinicians manage genotype results, it is much easier to have fewer bins and it is much less confusing for the clinician. So, there are incentives to 'keep it simple'. But it is not simple and CPIC should embrace the complexity for the reasons that follow. 2. Binning of phenotypes is highly reliant upon the accuracy of our understanding of the function of the individual alleles. This is complicated by substrate specificity (i.e. *10 may metabolize different drugs differently). *2 is a special case. *2 is presently classified as AS1 by CPIC. This is clearly not the case for all substrates but is likely true for some. Furthermore, the research done on *2 typically does not parse out *2A which has an AS>1. So the research done on *2 is a blend of individuals with *2 and *2A. This leads to an 'average' *2 activity and this may be leading to a spurious finding that *2's have an AS=1. CPIC should adopt binning per Mayo (similar to DPWG) and should 'call out' substrate specificity for specific alleles and drugs when known. 3. This discussion also hinges upon whether AS2 = AS1 clinically (i.e. referring to drug response and side effects here between the two categories). This is an easier discussion when therapeutic drug levels are a part of therapy because, in that situation, the drug levels are critical to patient care. Dividing AS1 and AS2 makes a clinical difference here because it impacts drug levels and clinicians/patients are interested in getting to the right drug level for therapeutic purposes. 4. Future state is also critical to this discussion. In the future, pharmacogenomic algorithms will manage allele activity scores and output drug binning accordingly. The actual stated 'phenotype' will be less relevant. 5. It should also be noted that NO other CYP enzyme phenotypes are binned like CYP2D6 is by CPIC. Now, there can be differences between isozymes in a family of genes, but classification of CYP2D6 differently than all other CYPs should only happen if there in incontrovertible evidence that this is necessary /appropriate and this is not the case here. In summary, I strongly favor a less reductionistic approach to CYP2D6 classification and strongly urge CPIC to adopt binning which shows the full spectrum of activity scores as detailed in Ji Y et al: Journal of Molecular Diagnostics 18 (3): 438-445, 2016. http://www.sciencedirect.com/science/article/pii/S1525157816000441.	4/15/2017 4:55 AM
16	The term ‘clinical significance’ is tricky, and in the spirit of clinical caution, we could assume that clinical significance may be observed when PK outcomes (e.g., differences in parent/metabolite ratios) are observed. However, there are data indicating that PK outcomes do not always lead to clinically significant outcomes (e.g., Fijal, 2015; PMID 25919121). This may be due to drug-drug interactions, impact of CYP2D6 metabolism on therapeutic activity/side effects, as well as other genetic and non-genetic factors . As such, let’s assume that PK outcomes have clinical significance. The data supporting a clinically significant difference between 1-2 mostly includes 1 = *10/*10, with assumption that *10 has AS = 0.5. However, *10 may be more like a AS = 0.25. As such, we should look at studies which are not biased for *10. As an example of a study in which *10 is not the only reduced function allele tested, Brown et al., 2016 shows that Activity score of 1 or 2 do not differ significantly for atomoxetine PK. Also, Vanwong et al., 2017 for risperidone. There may be some substrate-specificity since tamoxifen AS = 1 (IM/IM; EM/PM) (Hertz paper) does seem to show significant difference from AS=2 (EM/EM).	4/14/2017 10:54 AM

17	The majority of the comparator groups (Comparator 1 or Comparator 2) in the attached spreadsheet appear to consist of CYP2D6*10 alleles. Filtering on column I (*10 only analysis) and deleting those studies that did not directly compare an AS of 1 versus 2 (e.g., comparing 1-1.5 to 2), there are a total of 38 studies. 12 of the studies did not find a significant difference between AS 1 versus 2, where as 26 did. In total, there were 311 individuals (adding comparator 1 and comparator 2 sample size together) included in the studies that did not find a significant difference between AS 1 versus 2, with 754 individuals included in the studies that did find a significant difference. This is consistent with Hicks et al (PMID 24524666) that suggested there is a trend with those harboring CYP2D6*10 having lower CYP2D6 metabolic capacity than suggested by the assigned activity score. Filtering out CYP2D6*10 studies and those studies that did not directly compare AS of 1 versus 2 (e.g., comparing 1.5 to 2 or 0.5 to 2) there appears to be 22 studies left comparing AS 1 to AS 2. 13 studies did not find a difference between AS 1 versus 2, where 9 studies did find a statistical difference. The studies with the larger patient cohorts did not find a difference. In total, there were 2707 individuals (adding comparator 1 and comparator 2 sample size together) included in the studies that did not find a significant difference between AS 1 versus 2, with 555 individuals included in the studies that did find a significant difference. Based on sample size, overall there does not appear to be a difference between AS 1 versus AS 2 when CYP2D6*10 is not included in analysis. Clinically significant differences between AS 1 and 2 may be dependent on substrate. However, when taking into consideration substrate, the number of studies and cohort size becomes small making analysis challenging. For example, the studies involving tamoxifen did find significant differences between AS 1 versus 2. Most of the studies also included individuals harboring CYP2D6*10. It is difficult to differentiate if these differences are due to the substrate or the allele, or both. In summary, there appears to be a clinically significant difference between AS 1 versus AS 2 when CYP2D6*10 is included in analysis. There appears to be no major clinically significant differences for those studies where study subjects did not carry CYP2D6*10.	4/14/2017 1:45 AM
18	The relevant question is whether there is a conceivable situation where there is a clinically significant difference between a CYP2D6 activity score of 1 and 2. There are undoubtedly PK differences b/w an activity score of 1 and 2, as indicated by the overwhelming number of significant associations for these comparisons in the evidence review. With that in mind, it is undoubtedly conceivable that there will be a situation in which the difference b/w 1 and 2 is clinically meaningful. This could be a very narrow therapeutic drug, a drug with a 2D6 metabolite that is highly toxic, or a drug with a threshold effect where patients with AS=1 are therapeutic but patients with AS=2 are subtherapeutic. Given that there is clearly an identifiable kinetic difference b/w activity scores of 1 and 2 I am opposed to a system that unnecessarily collapses them at the level of the genotype-phenotype translation. Drugs for which the difference b/w 1 and 2 is not clinically relevant, the CPIC guidelines will indicate that patients with AS of 1 or 2 have similar treatment recommendations. In general, information should be lost or collapsed as little as possible early in the genotype->phenotype-> recommendation translation process.	4/11/2017 6:46 AM
19	Individual who are homozygous for CYP2D6*10 generally have decreased CYP2D6 activity. I do not think that individuals who are *1/*4 are different from those that are *1/*1. So, the problem is scoring *10 as 0.5, if *1 is 1 and normal is 1+.	4/9/2017 8:57 AM

Q2 Based on the current evidence (see attached spreadsheet and any additional studies you may be aware of), do you think there is a clinically significant difference between a CYP2D6 activity score of 0.5 and 1?

Answered: 27 Skipped: 0



Answer Choices	Responses	
Yes	**77.78%**	21
No	**22.22%**	6
Total		**27**

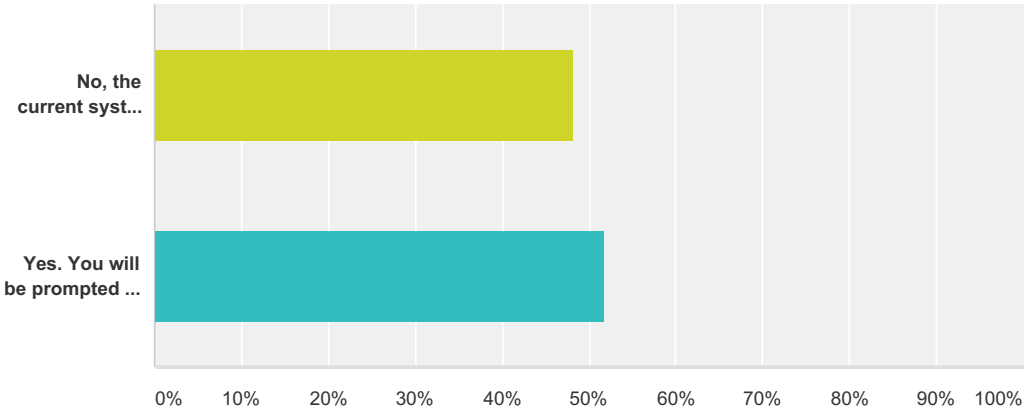
#	Please explain and provide references and examples that support your opinion.	Date
1	For drugs like codeine, an AS of 1 seems to be sufficient, whereas 0.5 is less convincing.	5/12/2017 9:19 AM
2	this is a critical question and there is not enough published evidence to currently support a difference between 0.5 and 1. However, this may be explained by the lack of power of all currently available studies. Future research is necessary to elucidate this issue.	5/4/2017 1:20 AM
3	In the spreadsheet more studies are presented that show no clinically significant difference between a score of 0.5 and 1. However, the studies that show a significant difference are bigger especially that of sachse et al (9012401), hinrichs et al (18553077) and hendset et al 24232129.	5/2/2017 2:49 AM
4	Dextromethorphan breath test (DM-BT) before and during tamoxifen therapy (77 patients) - % of DM-BT was significantly lower in patients with AS of 0.5 than those with AS of 1. Endoxifen levels were low in patients with low DM-BT having an AS of 0.5. PMID=25714002 (2015) Risperidone/9-hydroxyrisperidone is significantly higher in subjects with AS of 0.5 compared to those with AS of 2, however those with AS of 1 had similar parent/metabolite ratio than those with AS of 2. Table 6 PMID=26944100 (2016). Heart rate response to metoprolol was significantly different between subjects with AS=0.5 (IM) and those with AS of 1-2 (EM). PMID = 24637943 (2014)	5/1/2017 12:17 PM
5	Ruaño G, Szarek B, Villagra D, Gorowski K, Kocherla M, Seip RL, Goethe JW, Schwartz HI. Length of Psychiatric Hospitalization Correlated with CYP2D6 Functional Status in Inpatients with Major Depressive Disorder. Biomarkers in Medicine, 7 (3): 429-439, 2013 Villagra D, Goethe J, Schwartz HI, Szarek B, Kocherla M, Gorowski K, Windemuth A, Ruaño G. Novel Drug Metabolism Indices for Pharmacogenetic Functional Status Based on Combinatory Genotyping of CYP2C9, CYP2C19 and CYP2D6 Genes. Biomarkers in Medicine, 5 (4): 427-438, 2011 Ruaño G, Villagra D, Szarek B, Windemuth A, Kocherla M, Gorowski K, Berrezueta C, Schwartz HI, Goethe J. Physiogenomic Analysis of CYP450 Drug Metabolism Correlates Dyslipidemia with Pharmacogenetic Functional Status in Psychiatric Patients. Biomarkers in Medicine, 5 (4): 439-449, 2011 Functional phenotype: Poor	4/30/2017 11:13 PM
6	The excel sheet shows that for several drugs the pharmacokinetics dffers for those with an avtivity score of 0.5 vs 1.	4/28/2017 8:55 AM

7	I am not sure as I do not use activity scores. There is a difference in recommendations for those who are classified as intermediate metabolizers between CPIC and DPWG. If you look at codeine (CPIC) and tramadol (DPWG), someone who is for example *1/*5, this would be classified as a normal metabolizer for codeine, but an intermediate metabolizer for tramadol. So I am not sure if it is drug-specific or guideline group specific. Would love it to be harmonized.	4/24/2017 6:55 AM
8	I have stated "No" but its very line ball as some say Yes and others no. Again the differences are too subtle clinically- they might be statistically but likely clinically no difference. Is there anyway you can do a meta-analysis?	4/21/2017 10:25 AM
9	There is evidence that distinguishing between a phenotypic score of 0.5 (1 reduced and one no function allele) and 1 (one reduced and one normal, or two reduced function alleles) may be clinically relevant at least in substrates such as tamoxifen (1), risperidone (5,15), and carvedilol (8). As answered in the first question, we recommend keeping a classification of phenotypes as detailed as possible, to avoid discrepancies between studies and complicate interpretation when various genotype combinations are pooled in similar phenotype categories in the literature. 1. Hertz, D. et al. In vivo assessment of the metabolic activity of CYP2D6 diplotypes and alleles. British Journal of Clinical Pharmacology 80, 1122–1130 (2015). 5. Hendset, M., Molden, E., Knape, M. & Hermann, M. Serum Concentrations of Risperidone and Aripiprazole in Subgroups Encoding CYP2D6 Intermediate Metabolizer Phenotype. Ther Drug Monit 36, 80 (2014). 8. Sehrt, D., Meineke, I., Tzvetkov, M., Gültepe, S. & Brockmöller, J. Carvedilol pharmacokinetics and pharmacodynamics in relation to CYP2D6 and ADRB pharmacogenetics. Pharmacogenomics 12, 783–795 (2011). 15. Vanwong, N. et al. Impact of CYP2D6 Polymorphism on Steady-State Plasma Levels of Risperidone and 9-Hydroxyrisperidone in Thai Children and Adolescents with Autism Spectrum Disorder. Journal of Child and Adolescent Psychopharmacology (2016). doi:10.1089/cap.2014.0171	4/20/2017 10:03 AM
10	though less data support this difference to my opinion these groups should be separated	4/20/2017 8:05 AM
11	This is what I think the evidence to date shows. However, I do actually believe there will be a difference between 0.5 and 1 identified as we get more specific phenotype-substrate data in the future. The failure to demonstrate a difference in *10/*10 versus *10/*5 may be due to a mis-characterization of *10 as 0.5 activity score. Also, most of these studies have characterized *1 by default, which may lead to misclassification bias (Lim, 2011).	4/19/2017 6:48 AM
12	Among studies in which *10 is not the only decreased function allele, there appears to be evidence from multiple substrates that there is a significant difference in PK parameters between a CYP2D6 activity score of 0.5 and 1. The term ‘clinical significance’ is tricky, and in the spirit of clinical caution, we could assume that clinical significance may be observed when PK outcomes (e.g., differences in parent/metabolite ratios) are observed. However, there are data indicating that PK outcomes do not always lead to clinically significant outcomes (e.g., Fijal, 2015; PMID 25919121). As such, let’s assume that PK outcomes have clinical significance. In terms of implementation, it is simpler to assign metabolizer status by PK outcomes for most substrates, and then develop clinical alert content which may be substrate-specific. There does appear to a difference in PK parameters between activity score of 0.5 and 1 for aripiprazole (Hendset et al., 2014), dextromethorphan (Sachse et al., 1997), paroxetine (Chen et al., 2015), and atomoxetine (Brown et al., 2016).	4/18/2017 5:42 AM
13	I believe the overall effect of *4/*10 versus *10/*10 is broadly similar. A statistically significant difference can be obtained if sufficient individuals are studied but this seems unlikely to be relevant clinically. The Hertz et al. study seems the most useful reference of those you supplied in terms of this question though it would be useful to see more of their data to answer this question fully.	4/18/2017 1:33 AM
14	Activity appears to be substantially reduced when AS 0.5 is compared to AS 1. Hence, these genotypes should be grouped seperately. For some alleles, e.g. *10 (Tateishi et al), AS 0.5 and 1 genotypes are more similar raising concerns regarding *10 classification.	4/18/2017 1:29 AM
15	Subjects with genotypes giving rise to an AS of 1.0, which can be due to a diplotype containing one functional and one nonfunctional allele or containing two reduced-function alleles, are classified by some investigators as intermediate metabolizers by most commercial labs but as NM by CPIC. Regardless of the term used to describe such individuals (extensive or intermediate metabolizer), their CYP2D6 activity is lower as compared with subjects having two fully functional alleles (with an AS of 2.0) and higher as compared with subjects having one reduced and one nonfunctional allele (with an AS of 0.5). https://www.ncbi.nlm.nih.gov/pubmed/21412232 https://www.ncbi.nlm.nih.gov/books/NBK315951 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3975212/pdf/clpt2013254a.pdf	4/17/2017 8:38 AM
16	See my answer for Question 1.	4/15/2017 4:55 AM

17	Assuming that CYP2D6*10 activity score may not be representative of metabolic activity (based on my answer for question 1), studies (in the spreadsheet) comparing AS 0.5 to 1 that included subjects with CYP2D6*10 were excluded from consideration. Few studies are left, with a total of 10. Six studies (n=390 subjects) found a significant difference where as 4 studies (n=83 subjects) did not. Overall population numbers trends towards a difference. Based on my experience (literature reviews) with authoring CPIC guidelines, I believe that differences between AS 0.5 and 1 are likely to depend on substrate. There was a difference with PK paramaters for TCAs when comparing AS 0.5 to 1, but little evidence suggesting a difference between 0.5 to 1 for SSRIs. It should be noted that many studies do not clearly differentiate between AS 0.5 or 1, and in many instances are a mixed population. Thus, previously published data can be hard to analyze.	4/14/2017 2:01 AM
18	See answer to previous question. Again, there are PK differences b/w these groups that could be clinically relevant in some situations. I recommend designing a genotype->phenotype translation system that minimizes collapsing of activity scores.	4/11/2017 7:04 AM
19	Individuals that are *4/*10 have less activity than those that are *4/*1.	4/9/2017 8:58 AM

Q3 Are there CYP2D6 alleles where the activity score should be downgraded to AS of 0.25 or you think it is inappropriate to group them with other decreased function alleles?

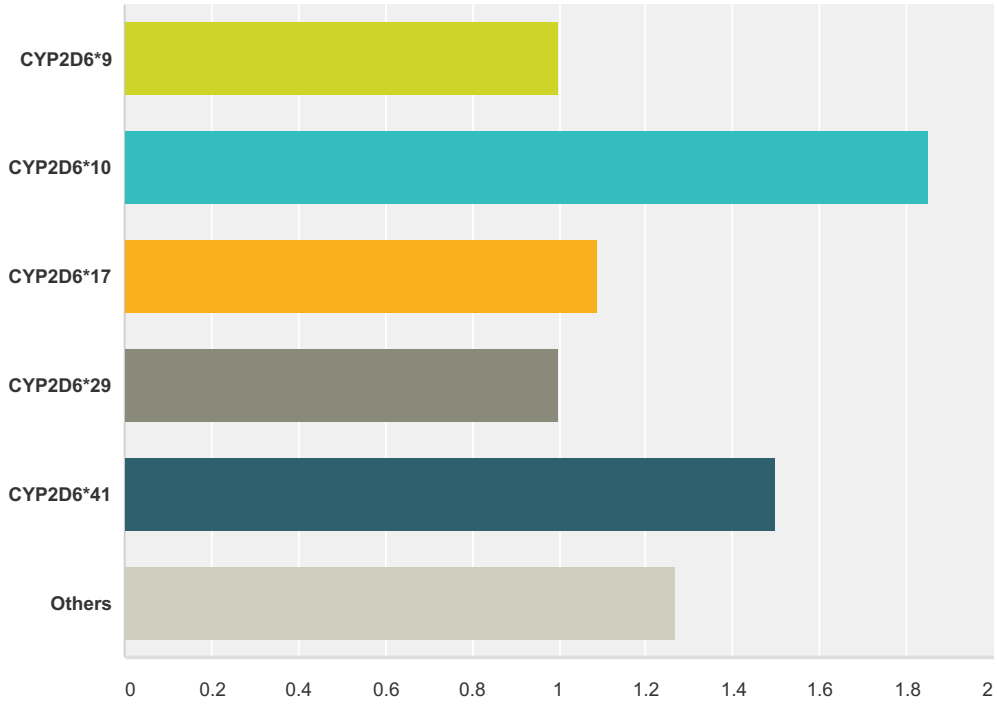
Answered: 27 Skipped: 0



Answer Choices	Responses
No, the current system of grouping all decreased alleles (e.g., *9, *10, *17, *29, *41, etc) together as an AS of 0.5 is adequate.	48.15% 13
Yes. You will be prompted on the next question to select alleles you believe should be downgraded to an AS of 0.25 or alleles in which the current grouping is not adequate.	51.85% 14
Total	**27**

Q4 Please select which CYP2D6 alleles you believe should be downgraded to an AS of 0.25 or alleles in which the current grouping is not adequate.

Answered: 14 Skipped: 13



	No	Yes	Total	Weighted Average
CYP2D6*9	**100.00%** 11	**0.00%** 0	11	1.00
CYP2D6*10	**15.38%** 2	**84.62%** 11	13	1.85
CYP2D6*17	**90.91%** 10	**9.09%** 1	11	1.09
CYP2D6*29	**100.00%** 10	**0.00%** 0	10	1.00
CYP2D6*41	**50.00%** 5	**50.00%** 5	10	1.50
Others	**72.73%** 8	**27.27%** 3	11	1.27

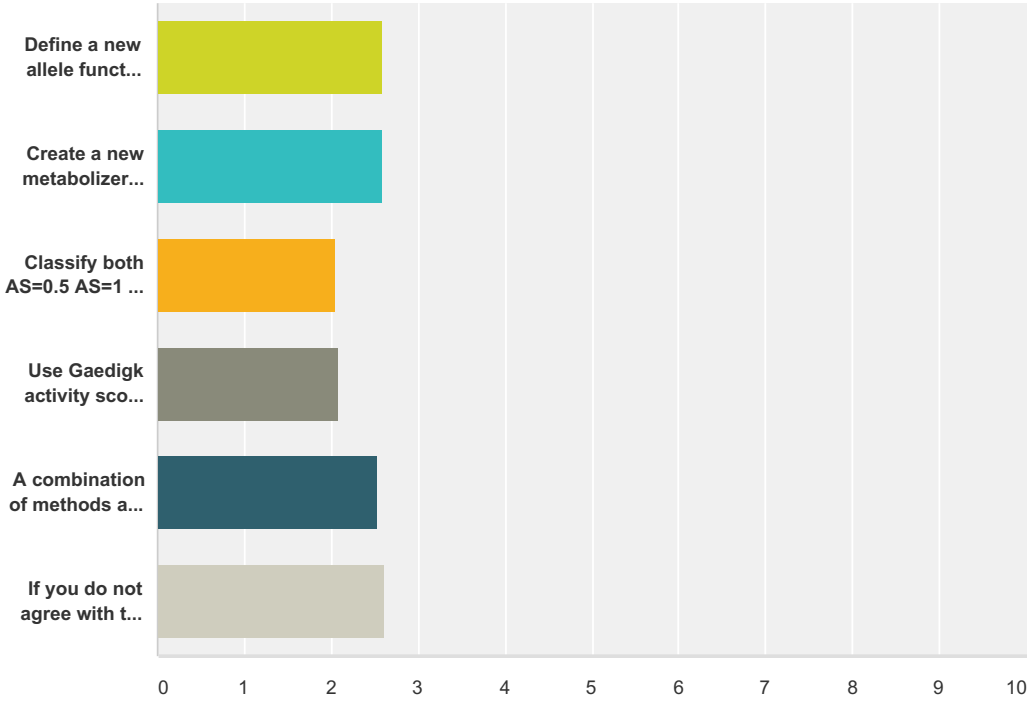
#	Comments for "CYP2D6*9"	Date
1	N/A	5/4/2017 1:23 AM
2	In the provide spreadsheet and pubmed searches I could not find studies that specifically show an alternate effect on clearance than described by Tyndale et al in 1991 and Broly & Meyer in 1993	5/2/2017 3:14 AM

3	Currently reporting at 0.5. Additional general comment for allele function determination: We do use a scoring based on available data. For example, if we find consistently in the literature that an allele has 30% of the activity of *1, and/or Vm/Km is 30% of *1, we give this allele a 0.3 activity. If data is less consistent (for example, function consistent with decrease activity across literature, but ranging from 20% to 70% of the wild type activity), we assign a 0.5 score. In other words, our approach is to be as representative of the biological activity as possible, normalized to wild-type. We are also investigating substrate-specific function. For example, CYP2D6*17 is typically considered a decreased function, however increasing evidence suggest that this allele is closer to a no-function allele for tamoxifen (1,14). Our interpretation system supports substrate specificity, so we are planning on implementing substrate-specific function. The main difference in our reporting approach is in calling “poor”, “slow” and “intermediate” metabolizer. In our methodology, we proceed as follows: - Poor: 2 no function alleles. - Slow: One no function allele, one decreased function allele. - Intermediate: One functional and one no function allele; or two decreased function alleles. - Normal: Two functional alleles. - Rapid: One functional allele and one increased function allele; or two increased function alleles, provided that the function of the alleles are between 1 and 1.5 - Ultrarapid: more than 3 functional alleles (multiplication) or two (or more) functional allele with function superior or equal to 1.5. Using these definitions for phenotypes, authors observed differences in patients for one or more pharmacokinetic parameters for tamoxifen(1) and risperidone (5). 1. Hertz, D. et al. In vivo assessment of the metabolic activity of CYP2D6 diplotypes and alleles. British Journal of Clinical Pharmacology 80, 1122–1130 (2015). 5. Hendset, M., Molden, E., Knape, M. & Hermann, M. Serum Concentrations of Risperidone and Aripiprazole in Subgroups Encoding CYP2D6 Intermediate Metabolizer Phenotype. Ther Drug Monit 36, 80 (2014). 14. Muroi, Y. et al. Functional characterization of wild-type and 49 CYP2D6 allelic variants for N-desmethyltamoxifen 4-hydroxylation activity. Drug Metab Pharmacok 29, 360–6 (2014).	4/20/2017 10:08 AM
4	Insufficient data on this allele to make a clear call.	4/18/2017 2:02 AM
5	There is no information supporting downgrading *9	4/18/2017 1:47 AM
6	I will answer for all alleles here. We do NGS and large panels so we call all alleles we see in CYP2D6. Please understand that some alleles have unknown function and we state that fact in our clinical reports when we find those alleles. We do use a scoring based on available data. For example, if we find consistently in the literature that an allele has 30% of the activity of *1 by whatever appropriate in vivo or in vitro lab parameter was studied, we assign 30% of *1, we give this allele a 0.3 activity. If data is less consistent, we assign a 0.5 score. We are also carefully evaluating substrate-specific function.	4/15/2017 4:55 AM
7	insufficient information	4/9/2017 9:08 AM
#	**Comments for "CYP2D6*10"**	**Date**
1	the Asian data for tamoxifen seems to support that they are different than 0.5.	5/12/2017 9:21 AM
2	based on linear modeling we could show that downgrade of *10 to 0.25 resulted into a better explanation of inter-individual variabilty with respect to plasma enoxifen concentrations in patients taking Tamoxifen.	5/4/2017 1:23 AM
3	In the spreadsheet the effect of the gene activity score seems to be larger in case of the *10/*10 genotype vs. the *1/*4 or *1/*5.	5/2/2017 3:14 AM
4	Currently reporting at 0.5.	4/20/2017 10:08 AM
5	*10 homozygous is clearly different from AS 1. subjects with this diplotype should receive a different dose. This could be achieved by providing a recommendation for AS 1 or by downgrading *10 to 0.25	4/20/2017 8:09 AM
6	*10 should be reduced to AS < 0.5 based on review conducted by Hicks et al., 2014. PMID:24524666	4/18/2017 5:42 AM
7	The extensive data available suggests this is essential.	4/18/2017 2:02 AM
8	Please see my answer to question 1. There appears to be significant differences regarding clinical parameters for those who harbor CYP2D6*10.	4/14/2017 2:04 AM
9	multiple Asian studies with multiple drugs	4/9/2017 9:08 AM
#	**Comments for "CYP2D6*17"**	**Date**
1	In the provide spreadsheet and pubmed searches I could not find studies that specifically show an alternate effect on clearance than described by Masimirembwa et al. (1996) and Oscarson et al (1997).	5/2/2017 3:14 AM
2	Currently reporting at 0.5. Currently investigating reporting at 0.1-0.3 (1,8,14) as for this allele in vivo and in vitro data point towards a lower function. 1. Hertz, D. et al. In vivo assessment of the metabolic activity of CYP2D6 diplotypes and alleles. British Journal of Clinical Pharmacology 80, 1122–1130 (2015). 8. Sehrt, D., Meineke, I., Tzvetkov, M., Gültepe, S. & Brockmöller, J. Carvedilol pharmacokinetics and pharmacodynamics in relation to CYP2D6 and ADRB pharmacogenetics. Pharmacogenomics 12, 783–795 (2011). 14. Muroi, Y. et al. Functional characterization of wild-type and 49 CYP2D6 allelic variants for N-desmethyltamoxifen 4-hydroxylation activity. Drug Metab Pharmacok 29, 360–6 (2014).	4/20/2017 10:08 AM

3	This is difficult. There is a comprehensive in vitro study (Shen H, He MM, Liu H, Wrighton SA, Wang L, Guo B, Li C. Comparative metabolic capabilities and inhibitory profiles of CYP2D6.1, CYP2D6.10, and CYP2D6.17. Drug Metab Dispos. 2007 Aug;35(8):1292-300. Epub 2007 Apr 30. PubMed PMID: 17470523) which suggests that for a number of different CYP2D6 substrates, CYP2D6*17 is unlikely to be as detrimental as CYP2D6*10). On the other hand, Hertz et al provide some indications that *17 has lower activity than *10 and recommend a lower scaling. More data needed on this allele to make a definitive recommendation in my view.	4/18/2017 2:02 AM
4	insufficient information	4/9/2017 9:08 AM
#	**Comments for "CYP2D6*29"**	**Date**
1	In the provide spreadsheet and pubmed searches I could not find studies that specifically show an alternate effect on clearance than described by (Marez et al., 1997; Wennerholm et al., 2001; Wennerholm et al., 2002)	5/2/2017 3:14 AM
2	Currently reporting at 0.5.	4/20/2017 10:08 AM
3	Data too limited though Hertz et al. provide some indication that downgrading may be justified.	4/18/2017 2:02 AM
4	insufficient information	4/9/2017 9:08 AM
#	**Comments for "CYP2D6*41"**	**Date**
1	In the provide spreadsheet and pubmed searches I could not find studies that specifically show an alternate effect on clearance than described by (Raimundo et al., 2000, Raimundo et al., 2004, Toscano et al., 2006, Rau et al., 2006)	5/2/2017 3:14 AM
2	Currently reporting at 0.5.	4/20/2017 10:08 AM
3	There is sufficient data (Hertz et al. plus Raimundo S, Fischer J, Eichelbaum M, Griese EU, Schwab M, Zanger UM.Elucidation of the genetic basis of the common 'intermediate metabolizer' phenotype for drug oxidation by CYP2D6. Pharmacogenetics. 2000 Oct;10(7):577-81. PubMed PMID: 11037799.) to demonstrate the low activity associated with this allele. Because this is quite a common allele in Europeans, finding data to support downgrading is not too difficult.	4/18/2017 2:02 AM
4	Candidate to further explore. Abduljalil et al (PMID 20881950) indicated that "The clearance attributable to an individual CYP2D6*1 copy was 2.5-fold higher as compared with CYP2D6*2 (5,010 vs. 2,020 l/h), whereas the metabolic activity of CYP2D6*41 was very low (85 l/h).	4/18/2017 1:47 AM
5	I think the phenotype is comparable to *10.	4/9/2017 9:08 AM
#	**Comments for "Others"**	**Date**
1	Other alleles harboring the 100C>T (tag snp for *10) such as tandem *10-36.	5/1/2017 12:18 PM
2	*2: Reporting at 0.6 (1,8,14,17) *2A: Currently reporting at 1.4 (18,19) 1. Hertz, D. et al. In vivo assessment of the metabolic activity of CYP2D6 diplotypes and alleles. British Journal of Clinical Pharmacology 80, 1122–1130 (2015). 8. Sehrt, D., Meineke, I., Tzvetkov, M., Gültepe, S. & Brockmöller, J. Carvedilol pharmacokinetics and pharmacodynamics in relation to CYP2D6 and ADRB pharmacogenetics. Pharmacogenomics 12, 783–795 (2011). 14. Muroi, Y. et al. Functional characterization of wild-type and 49 CYP2D6 allelic variants for N-desmethyltamoxifen 4-hydroxylation activity. Drug Metab Pharmacok 29, 360–6 (2014). 17. Sakuyama, K. et al. Functional Characterization of 17 CYP2D6 Allelic Variants (CYP2D6.2, 10, 14A–B, 18, 27, 36, 39, 47–51, 53–55, and 57). Drug Metab Dispos 36, 2460–2467 (2008). 18. Serrano et al. Efficacy of tamoxifen based on cytochrome P450 2D6, CYP2C19 and SULT1A1 genotype in the Italian Tamoxifen Prevention Trial. Pharmacogenomics J 11, 100–107 (2010). 19. Villagra, D. et al. Novel drug metabolism indices for pharmacogenetic functional status based on combinatory genotyping of CYP2C9, CYP2C19 and CYP2D6 genes. Biomark Med 5, 427–438 (2011).	4/20/2017 10:08 AM
3	It is very difficult to make general recommendations concerning rare alleles.	4/18/2017 2:02 AM
4	Sakuyama et al (PMID: 18784265) describe a number of variants (e.g.*48, *49, *50, etc) with activity towards bufuralol that is comparable to *10. Additional low activity alleles have been described by Dai et al (PMID: 25469868) e.g. *89 and *93. This group also published a series of additional papers using other substrates	4/18/2017 1:47 AM
5	Activity of individual alleles is not my expertise. From my studies and the literature it seems that *2 is not a fully active allele and that duplications do not truly duplicate the activity (i.e. 2x).	4/11/2017 7:08 AM
6	insufficient evidence	4/9/2017 9:08 AM

Q5 The options below contain methods currently being used by genetic testing laboratories to translate CYP2D6 genotype to phenotype. Please describe your degree of acceptance to the following methods and explain and provide references and examples that support your opinion.

Answered: 27 Skipped: 0



	Strongly Disagree	Disagree	Agree	Strongly Agree	Total	Weighted Average
Define a new allele function group (e.g. “severely decreased” or “low” function); alleles will receive a value of 0.25 to calculate the AS (We will first identify alleles falling into this category and then create addition AS groups (0.25, 0.75, 1.25, and 2.25) which will need to be categorized).	**7.41%** 2	**37.04%** 10	**44.44%** 12	**11.11%** 3	27	2.59
Create a new metabolizer phenotype category for AS=0.5 genotypes ((e.g. “severely decreased” or “low” function). Genotypes with an AS=1 (*10/*10, *9/*9, *1/*4, etc) would be classified as Intermediate Metabolizers.	**7.41%** 2	**44.44%** 12	**29.63%** 8	**18.52%** 5	27	2.59
Classify both AS=0.5 AS=1 as Intermediate Metabolizers. AS=0.5 and 1 genotypes would receive the same recommendation	**29.63%** 8	**48.15%** 13	**11.11%** 3	**11.11%** 3	27	2.04
Use Gaedigk activity score, as is but have separate recommendations based on AS. AS of 1-2 will still be Normal Metabolizers, but recommendations might be different based on AS (or even genotype-specific?).	**32.00%** 8	**32.00%** 8	**32.00%** 8	**4.00%** 1	25	2.08
A combination of methods a and c above. Some alleles would receive a lower AS and we would create an additional phenotype group between Intermediate Metabolizer and Poor Metabolizer (e.g. “severely decreased” or “low” function).	**14.81%** 4	**40.74%** 11	**22.22%** 6	**22.22%** 6	27	2.52
If you do not agree with the above option, please provide an alternative.	**20.00%** 2	**30.00%** 3	**20.00%** 2	**30.00%** 3	10	2.60

#	Comments for "Define a new allele function group (e.g. “severely decreased” or “low” function); alleles will receive a value of 0.25 to calculate the AS (We will first identify alleles falling into this category and then create addition AS groups (0.25, 0.75, 1.25, and 2.25) which will need to be categorized). "	Date
1	For PK associations I think it would be valuable. In some cases, maybe also for clinical implementation.	5/12/2017 9:30 AM
2	Based on this you would be able to provide an alternate dosing for the *10/*10 heterozygous cariers (which would receive a score of 0.5) compared to heterozygous carriers of a nonfunctional allele. However, this would probably complicate the interpretation of genetic test result for clinicians even furter and would warrant a lot more new dosing recommendations.	5/2/2017 3:36 AM
3	we have categorized alleles in groups but in fact it is a continuous scale; more groups will not solve this problem	5/1/2017 6:14 PM
4	I am concerned the finer gradation will confuse the field.	4/30/2017 11:15 PM
5	this seems like too much over classification to me. Because I am not sure where the cut off is.	4/24/2017 7:06 AM
6	For clinicians, the current system is already complex. We have poor, intermediate and normal. No more categories, also because already we are seeing big overlaps. So for clinical utility, I would recommend no further subgrading.	4/22/2017 1:37 AM
7	Low function seems reasonable but differentiating 0.25 and 0.5 will be difficult. My view is to keep it simple	4/21/2017 10:31 AM
8	Agreed with the idea of giving alleles scores below 0.5 and scores that may be more “linear” and reflect activities observed in vivo.	4/20/2017 10:10 AM
9	though this may be the most scientifically sound appraoch I do not think it is clinically feasible. Also I'm not convinced that some of the AS differences translate into meaningfull differences in clinical outcomes	4/20/2017 8:15 AM
10	The problem here is that these decreased activities are likely substrate dependent. Therefore, we can't uniformly downgrade alleles without a reference phenotyping method. Until that has been adequately studied/established, I would not favor altering the granularity of these designations since we don't have a good reference. You can be right about and activity score 0.25 when talking about dextromethorphan but wrong when considering codeine, as an example.	4/19/2017 7:08 AM
11	However, this leads to the question of how phenotypes will be categorized. A solution that includes AS = 0.25 and a new phenotype categorization would be better (last choice below).	4/18/2017 8:59 AM
12	This option would allow to more accurately group subjects with reduced function alleles.	4/18/2017 7:07 AM
13	I don't like the AS system. This appears to have been developed without extensive discussion internationally and has now led to problems. An activity score of 2.25 is likely to confuse further.	4/18/2017 2:20 AM
14	Creating additional AS groups (0.25, 0.75. 1.25 and 2.25) might result in additional NM to URM, IM to NM, PM to IM categories which could be more confusing to providers	4/17/2017 8:39 AM
15	I am just going to give you our interpretation table here as opposed to doing these one by one. It is a little messy so if you need a file sent to you, just tell me. The article listed below used these ranges to derive the phenotypes shown in the article's Table 2. 'x' represents the AS of the genotype and if it falls within a given range, the phenotype is called. Ultrarapid AS≥3, Rapid AS 2.25. See: Ji Y et al: Journal of Molecular Diagnostics 18 (3): 438-445, 2016.	4/15/2017 4:55 AM
16	For those individuals who are CYP2D6*10, it appears that CYP2D6 metabolic capacity may be overestimated by the activity score. Please see previous answers for support of this statement. CYP2D6*10/*10 may fit better in the intermediate metabolizer phenotype. Adjusting allele function groups (e.g., 0.25) will theoretically provide more granularity for calculating AS score and thus phenotype assignment. For example, CYP2D6*10, CYP2D6*17, CYP2D6*9, and CYP2D6 *41 likely do not have the same metabolic activity, with certain alleles (CYP2D6*10) having lower metabolic activity and certain alleles (CYP2D6*41/*17) having higher metabolic activity. Adjusting allele function group may allow CYP2D6*10 homozygotes to flow into IM status where as CYP2D6*41 homozygotes would be EMs.	4/14/2017 3:01 AM
17	The less we lose information at the stage of allelic activity assignment, the better off we are when it comes to creating a single system that can accommodate all drugs and recommendations.	4/11/2017 7:09 AM
18	I don't think we need the additional AS groups. We can use 0, 0.25-0.5, 1-2, >2.	4/9/2017 9:11 AM
#	**Comments for "Create a new metabolizer phenotype category for AS=0.5 genotypes ((e.g. “severely decreased” or “low” function). Genotypes with an AS=1 (*10/*10, *9/*9, *1/*4, etc) would be classified as Intermediate Metabolizers. "**	**Date**
1	particularly for Asians, this would likely be useful.	5/12/2017 9:30 AM
2	I understand this is controversial but would prefer we avoid this if possible.	5/9/2017 7:39 AM
3	Based on this proposal you would not be able to distinguish the *10 allele from other alleles with an impaired function such as *9 and *41.	5/2/2017 3:36 AM

4	We should aim for functional definitions. Our laboratory currently uses Null, Poor, Deficient, Functional, Supra-functional.	4/30/2017 11:15 PM
5	this is where I would like to see harmonization between CPIC and DPWG. I do think that if someone is taking a CYP2D6 inhibitor then you can see a difference.	4/24/2017 7:06 AM
6	I would favor this over having *10/*10 etc as normal metabolizer, as is stated now. But still would categorize them all in 1 group, bewteen deficient/poor and normal. So intermediate (for reasons, see above)	4/22/2017 1:37 AM
7	the examples such as *10/*10 seem reasonable	4/21/2017 10:31 AM
8	Agreed with a “slow metabolizer” category, defined by two severely decreased function alleles, or by a no function allele and a decreased function allele. Two decreased function alleles would be considered intermediate. Please see other answers for references.	4/20/2017 10:10 AM
9	This option adds just enough categories to make in clinically feasible as well as adress differences that are large enough to translate into clinical differences	4/20/2017 8:15 AM
10	This assumes that there is a difference between 0.5 and 1.0 activity score. I don't think the literature supports that currently. Ultimately this scale may be on a continuous scale, though I don't think we have enough data to support a new category at this juncture.	4/19/2017 7:08 AM
11	Since there is no significant difference between AS 1 and AS2 (see answer to survey question 1), AS1 classification as Intermediate Metabolizer would not be supported.	4/18/2017 8:59 AM
12	The advantage of this option is to categorize *1/*4 for example as IM, which is more in line with the categorization of other CYPs. The downside is that *10/*10 would not be in the 'severely decreased' category.	4/18/2017 7:07 AM
13	Any new system must distinguish between *1/*4 and *10/*10. The activity associated with these genotypes is not the same. *10/*10<<*1/*4 in almost all studies provided where both genotypes are available in sufficient numbers to make clear conclusions. In my view, a *1/*4 individual is not an intermediate metabolizer and should be classed as an extensive metabolizer.	4/18/2017 2:20 AM
14	Having Genotypes with an AS = 1 will be consistent with DPWG and most commercial labs.	4/17/2017 8:39 AM
15	Referring to answer number 1, there does not appear to be a clinically significant difference between AS 1 versus AS 2 if CYP2D6*10 allele is excluded from analysis. This also does not solve the issue of whether CYP2D6*10/*10 should be an AS of 1 or 0.5 An initial approach would be developing new allele function groups and modeling out what how phenotype assignments would change. There will be challenges regarding phenotype assignment for 0.25 and 0.75. If it is clear that 0.25 or 0.75 do fit into a phenotype assignment (IM or EM), or if it becomes clear that there are other challenges with phenotype assignment, then consideration should be given to a new phenotype group. It would likely be more prudent to adjust allele function groups first, then based on modeling (if phenotype assignments cannot be clearly made) to develop a new phenotype group.	4/14/2017 3:01 AM
16	HERTZ et al. Goetz ABCSG 8 Clin Canc Res 2014	4/13/2017 7:51 AM
17	too complicated	4/9/2017 9:11 AM
#	**Comments for "Classify both AS=0.5 AS=1 as Intermediate Metabolizers. AS=0.5 and 1 genotypes would receive the same recommendation "**	**Date**
1	For clinical recommendations for most drugs, 1.0 is similar to 2.0.	5/12/2017 9:30 AM
2	Based on my interpretation of the provided spreadsheet there appears to be a difference between an AS of 0.5 and 1. With this method you would not be able to distinguish between the two scores.	5/2/2017 3:36 AM
3	We phenotype a score of 0.5 as Poor function.	4/30/2017 11:15 PM
4	There are less studies on AS 0.5. Perhaps in the future it will appear that for several more drugs the dufference between 0.5 and 1 is clinically relevant. Therefore we have to classify them differently.	4/28/2017 9:09 AM
5	this is where I would like to see harmonization between CPIC and DPWG. I do think that if someone is taking a CYP2D6 inhibitor then you can see a difference.	4/24/2017 7:06 AM
6	For clinicians, the current system is already complex. We have poor, intermediate and normal. No more categories, also because already we are seeing big overlaps. So for clinical utility, I would recommend no further subgrading.	4/22/2017 1:37 AM
7	The differences are too small in my opinion	4/21/2017 10:31 AM

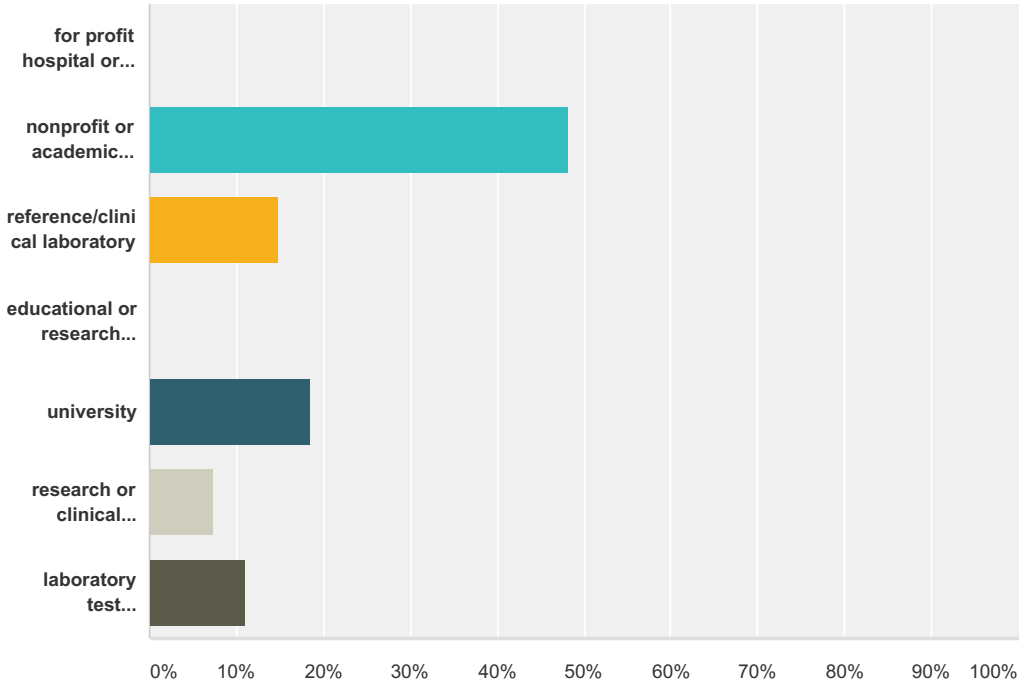
8	Disagree. Does not account for variations in phenotypes observed in patients (1,5,8). 1. Hertz, D. et al. In vivo assessment of the metabolic activity of CYP2D6 diplotypes and alleles. British Journal of Clinical Pharmacology 80, 1122–1130 (2015). 5. Hendset, M., Molden, E., Knape, M. & Hermann, M. Serum Concentrations of Risperidone and Aripiprazole in Subgroups Encoding CYP2D6 Intermediate Metabolizer Phenotype. Ther Drug Monit 36, 80 (2014). 8. Sehrt, D., Meineke, I., Tzvetkov, M., Gültepe, S. & Brockmöller, J. Carvedilol pharmacokinetics and pharmacodynamics in relation to CYP2D6 and ADRB pharmacogenetics. Pharmacogenomics 12, 783–795 (2011).	4/20/2017 10:10 AM
9	this is the current DPWG system -- to my opinion and based on the evidence provided AS 0.5 and 1 should be separated	4/20/2017 8:15 AM
10	These designations have most accurately described our own phenotyping experiments. The major limitation in most of these phenotyping studies to date are failure to capture enough variants which ultimately defaults to *1. Steimer, 2004 demonstrated a difference in these activity scores from NMs (known as EMs during that study), Xiang, 2010 and Suzuki 2013, also demonstrated this.	4/19/2017 7:08 AM
11	There appears to be a significant difference between AS 0.5 and AS 1 (see survey question 2), so it does not make sense to classify both as the same phenotype.	4/18/2017 8:59 AM
12	examples shown in the call strongly support the notion that AS 0.5 especially *10/null genotypes are distinct, and that clinical recommendation should reflect the severely reduced function status.	4/18/2017 7:07 AM
13	Again, this does not distinguish between those homozygous for *10 and those heterozygous for *4 etc which is crucial.	4/18/2017 2:20 AM
14	It will be consistent with DPWG and most commercial labs.	4/17/2017 8:39 AM
15	Excluding CYP2D6*10 and based on CPIC guidelines, there appears to be differences between AS 0.5 and 1, but potentially less differences between AS 1 and 2. It is not clear if grouping AS 0.5 and AS 1 into a phenotype would be of clinical benefit.	4/14/2017 3:01 AM
16	HERTZ et al	4/13/2017 7:51 AM
17	Too much loss of information given the established differences in activity and drug PK	4/11/2017 7:09 AM
18	*1/*4 is not intermediate	4/9/2017 9:11 AM
#	**Comments for "Use Gaedigk activity score, as is but have separate recommendations based on AS. AS of 1-2 will still be Normal Metabolizers, but recommendations might be different based on AS (or even genotype-specific?)."**	**Date**
1	I would be ok with this.	5/12/2017 9:30 AM
2	Genotype specific (instead of phenotype specific) would be very difficult in clinical practice as 1) clinicians often just grasp the concept of phenotypes but would get lost in case genotypes they should enter genotypes in their systems and 2) In most cases only the phenotype is entered in the clinical decision support systems and the original genotype is very hard to retrieve and would require a reprogramming of the systems in which a lot of information would get lost.	5/2/2017 3:36 AM
3	AS should have unique names.Numers are not very clear for those who are less familiar with the topic.	4/28/2017 9:09 AM
4	Now I am really confused since I do not use activity scores..... seems to make sense.....but then again, I am confused	4/24/2017 7:06 AM
5	It seems that we finally have clinicians able to work with normal, intermediate and poor as predicted phenotypes after many, manty years. Activity scores would perhaps not have the same effect, but I realize it may just be a changing process. In addition, i feel that the activity scores may suggest a subdivision which is not clinically justified: already we see big overlap in groups, which depends on substrate used and concentration of the drug.	4/22/2017 1:37 AM
6	not just genotype specific but drug specific. I think this is important to make the score's interpretation drug specific.	4/21/2017 10:31 AM
7	It seems that this approach amounts to using AS instead of phenotype categories to provide recommendations, which would be confusing. Using separate phenotype categories for different AS would be clearer. I agree however that depending on the substrates, therapeutic recommendations could be the same for two different phenotypes (example: paroxetine in intermediate and normal metabolizers).	4/20/2017 10:10 AM
8	Again, I believe AS of 1 and 2 are different. As demonstrated by Xiang, Suzuki, Steimer, and Parker (which isn't included in your table: PMID: 21923449).	4/19/2017 7:08 AM
9	Current implementation approaches do not have Therapeutic recommendations based on AS (PMID: 27864204), and so that would have to be developed.	4/18/2017 8:59 AM
10	might be too confusing to make recommendations based on AS, but still use existing phenotype classifications	4/18/2017 7:07 AM
11	Don't understand this option.	4/18/2017 2:20 AM

12	It would be impossible to drive CDS where EMs have 2 different recommendations. Having an AS 1 - normal metabolizer with a dose change and AS 2 - normal metabolizer with no dose change is absolutely too complicated for clinical practice, as based on my experience with clinical implementation. ****Remember not all genes have an activity score, so this would require additional discrete data curation in the EHR as phenotype would still be needed for other genes such as CYP2C19**** A new phenotype, if needed, would be a much more acceptable approach. At some point genotype has to be translated into a clinical action. Based on tablet sizes and the ability to cut pills and available dosage forms,there are only so many practical clinical recommendations (e.g., 50% dose reduction, 25% reduction, etc). I don't see a reason why these limited practical recommendations cannot be captured by phenotype groups. At the moment, genotype-based CDS would be almost impossible for most institutions. The number of rules needed to mange genotype-driven (and not phenotype drive) would be in the 1000s for a gene like CYP2D6. How would CPIC guidelines function at the level of genotype-specific recommendations instead of phenotype?	4/14/2017 3:01 AM
13	It defeats the purpose of the system to have a single phenotype with different recommendations. If the end-user needs to have the AS# or the specific genotype, what's the point in assigning a phenotype category?	4/11/2017 7:09 AM
14	too complicated	4/9/2017 9:11 AM
#	**Comments for "A combination of methods a and c above. Some alleles would receive a lower AS and we would create an additional phenotype group between Intermediate Metabolizer and Poor Metabolizer (e.g. “severely decreased” or “low” function). "**	**Date**
1	based on linear modelling of patients treated with Tamoxifen, a definition of "slow metabolizers" with acitivity score of .25 to .5 resulted into a model which better explained inter-individual variability of active metabolite concentration (Endoxifen).	5/4/2017 1:33 AM
2	Based on this method you would be able to downgrade specific alleles (especially *10, as provided evidence shows that the homozygous carriers of the *10 alleles seem to have a lower activity than heterozygous carries of nonfunctional alleles). Based on this you could differentiate in heterozygous carries from heterzygous carriers of a nonfunctional allele.	5/2/2017 3:36 AM
3	I suggest we discuss a difference between Poor and Null. Null is the most severe phenotype: no function.	4/30/2017 11:15 PM
4	seems like too much work to split this up so much. Does it make a clinical difference? Essentially you are lumping results together and using to predict a phenotype and estimate the amount of drug to prescribe (or not to prescribe). It is an estimate and not an exact science because there are other genes/protein variation that can affect this prediction. It is a like head lights when you are driving....there is still a lot out there that you cannot see. I think that we are trying to split hairs where it does not make sense.	4/24/2017 7:06 AM
5	Low function is OK but may need to be drug specific	4/21/2017 10:31 AM
6	Agreed, please see the justification in first two questions from survey. “Slow” metabolizers could or should be defined by 0 < AS ≤ 0.5, or one defective allele with a no function allele, or two alleles with AS ≤ 0.25.	4/20/2017 10:10 AM
7	this system is too complex	4/20/2017 8:15 AM
8	This is consistent with data indicating differences in PK parameters between AS = 1 and AS = 0.5.	4/18/2017 8:59 AM
9	Too many groups proposed. Intermediate would become unnecessary in this situation.	4/18/2017 2:20 AM
10	Too many phenotype categories.	4/17/2017 8:39 AM
11	It would likely be more prudent to adjust allele function groups first, then based on modeling (if phenotype assignments cannot be clearly made) to develop a new phenotype group.	4/14/2017 3:01 AM
12	Too much loss of information	4/11/2017 7:09 AM
13	too complicated	4/9/2017 9:11 AM
#	**Comments for "If you do not agree with the above option, please provide an alternative."**	**Date**
1	Concerned about overly complicating the genotype to phenotype system and having too many categories.	5/18/2017 2:50 PM
2	Let us please discuss rapid alleles *35 and *2a. Also, I suggest RANKING of the CYP2D6 function in a continuum based on population surveys. Patients can then be profiled by their position in the distribution as a quantitative percentile. This will do away with qualitative binning, and provide a quantitative result.	4/30/2017 11:15 PM
3	Yikes....see above.	4/24/2017 7:06 AM

4	An issue with standardization of phenotype naming is substrate- or genotype-specificity. This is a difficult problem to address but I suggest that phenotypes from genotypes with a substrate-specific allele should be specified, in other words that the phenotype should be called for each substrate. For example, we have found that calling CYP2C9 *2/*2 a “poor metabolizer” as a general statement is highly misleading and not accurate for substrates like warfarin, celecoxib, flurbiprofen, glimepiride or glyburide. A suggestion would be to call a phenotype for a specific medication, for example: “CYP2C9 *2/*2: Substrate-specific: poor metabolizer of phenytoin, intermediate metabolizer of warfarin”. (Apologies, I have so far better examples regarding CYP2C9*2 than for CYP2D6 at this point).	4/20/2017 10:10 AM
5	Thank you, good discussion points. I summarize this by saying AS must be standardized on a single reference substrate or else we will be wrong in phenotype prediction. I believe that the AS will ultimately mature to eliminate the relatively artificial 4 discreet haplotype groups but we are not there yet. For now, I believe the data supports staying with 4 groups, 0, 0.5-1.49, 1.5-2.5, and greater than 2.5.	4/19/2017 7:08 AM
6	Ultrarapid metabolizer: 4 or more active CYP2D6 alleles Extensive metabolizer: homozygous for *1 and *2; heterozygous for almost any variant; 3 active CYP2D6 alleles Intermediate (or impaired) metabolizer: homozygous for *10 or *41; *4/*10 and similar genotypes; possibly also homozygous for *9 and *17 but currently insufficient data. Poor metabolizer: homozygous for any combination of loss of activity allele. This is supported by some of the original literature e.g. Dalen et al; Sachse et al, Hertz et al plus several of the studies on *10 from East Asia.	4/18/2017 2:20 AM
7	Classify both AS=0.5 AS=1 as Intermediate Metabolizers.	4/17/2017 8:39 AM
8	n/a	4/13/2017 7:51 AM
9	The need to translate continuous data into ordinal scales using arbitrary thresholds is a relic from pre-EMR times. An ideal system would assign each patient a percent activity score that gets scaled to 1.0 or 100% (current AS=2) that would be intuitive to clinicians. Treatment recommendations can then be based on scaled activity. Since we have the worlds experts in this group, and likely access to the majority of relevant datasets, we should set out to empirically define the activity score for each individual allele using in vivo datasets (See Hertz et al. PMID: 24648760) or well controlled in vitro experiments. We should then work forward toward creating guidelines that translate a patient's scaled activity into appropriate dosing or treatment recommendations. Importantly, if there is meaningful substrate dependence (i.e. an individual allele is low activity for one substrate but high activity for another), then the entire activity score model needs to be reconsidered. The information in the evidence review is not sufficient to determine whether this is the case, but it's a testable hypothesis that could be answered using the available datasets.	4/11/2017 7:09 AM

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

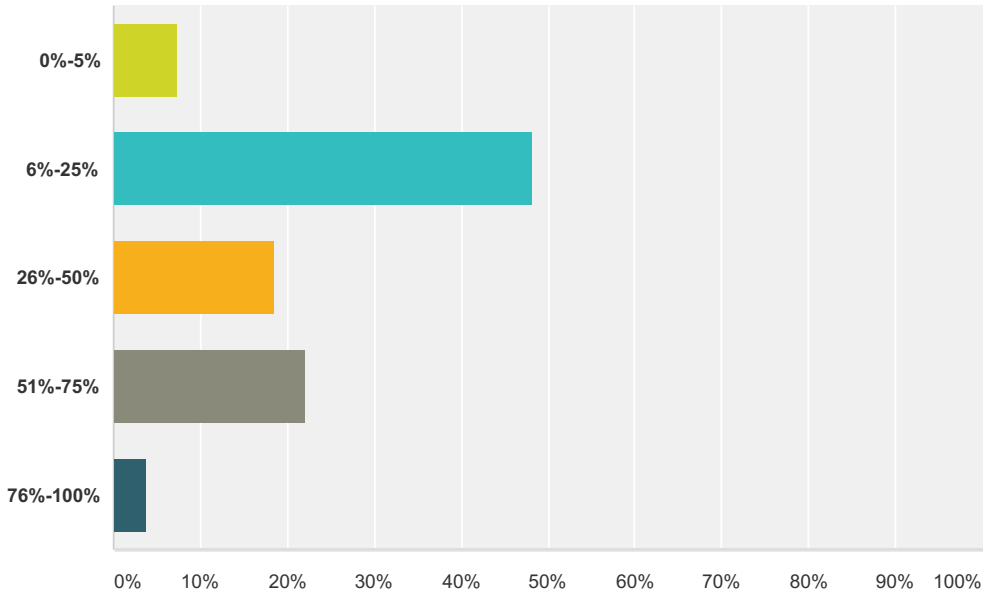
Answered: 27 Skipped: 0



Answer Choices	Responses	
for profit hospital or clinic	**0.00%**	0
nonprofit or academic hospital or clinic	**48.15%**	13
reference/clinical laboratory	**14.81%**	4
educational or research resource	**0.00%**	0
university	**18.52%**	5
research or clinical institute	**7.41%**	2
laboratory test interpretation service	**11.11%**	3
Total		**27**

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

Answered: 27 Skipped: 0



Answer Choices	Responses	
0%-5%	**7.41%**	2
6%-25%	**48.15%**	13
26%-50%	**18.52%**	5
51%-75%	**22.22%**	6
76%-100%	**3.70%**	1
Total		**27**