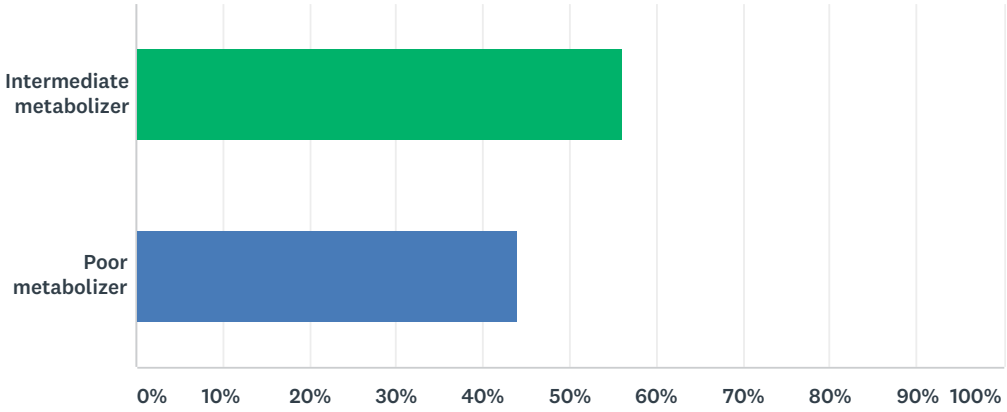
Q1 Do you think an AS of 0.25 should be grouped as an IM or PM? Examples of AS of 0.25 include: CYP2D6*4/*10; *5/*10

Answered: 25 Skipped: 0



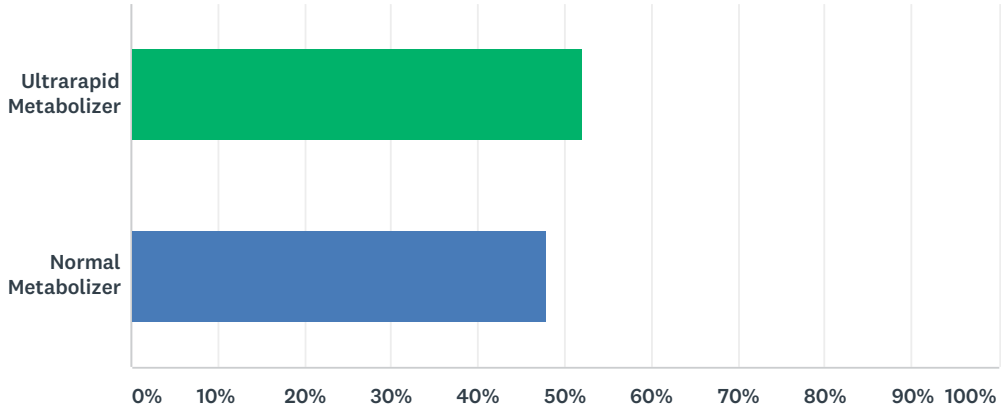
ANSWER CHOICES	RESPONSES	
Intermediate metabolizer	56.00%	14
Poor metabolizer	44.00%	11
TOTAL		25

#	WHY DO YOU THINK THE OPTION YOU CHOSE IS PREFERABLE?	DATE
1	In the end I expect that the dosing advice for a PM will be more appropriate that the dosing advice for an IM.	4/2/2018 4:19 PM
2	PM should be reserved for those with 2 no activity alleles.	4/2/2018 7:22 AM
3	Based on the PK data(please see the below ref and other groups) and the publication of clinical outcome of patients with CYP2D6 null/*10 after tamoxifen therapy, they should be classified into CYP2D6 null/null group. Dose-adjustment study of tamoxifen based on CYP2D6 genotypes in Japanese breast cancer patients.Kiyotani K, et al.Breast Cancer Res Treat. 2012 Jan;131(1):137-45.	3/31/2018 11:05 PM
4	Patients with *4/*10; *5/*10 were previously categorised as Intermediate metabolizers. Currently, limited PK data is available on how to dose patients with a combination of a null allele and a *10 allele and categorizing them as poor metabolizer might lead to undertreatment.	3/30/2018 10:22 AM
5	Inherently, there is some metabolic activity with these variants so I believe this is more consistent with the language and the intent. PMs should be truly deficient in enzyme activity.	3/29/2018 3:34 PM
6	IM is broad group/range	3/29/2018 5:43 AM
7	Because there is some remaining activity. Poor metabolizers for CYP2D6 have zero.	3/28/2018 12:40 PM
8	The *10 allele appears to have decreased function compared to other alleles such as *17 or *41. Also, having an AS of 1-0.25 representing intermediate metabolizers appears to be a wide range of activity within one phenotype.	3/28/2018 7:46 AM
9	Making 0.25 as IM means that *4/*10 and *1/*4 would be considered as having the same phenotype, which is inaccurate. Ideally, I still support a "slow metabolizer" group to be able to provide substrate-specific recommendation that are less confusing.	3/27/2018 8:20 PM
10	Let us be clear to define POOR as NULL -- ZERO activity	3/27/2018 12:41 PM
11	I think they should be called PM to IM. I will elucidate more later.	3/27/2018 10:24 AM
12	Because is significantly different from AS 0 (PM)	3/27/2018 12:41 AM

13	Because PMs are defined as two no function alleles	3/26/2018 7:16 PM
14	I think there should be some low activity. For me a PM, is no activity	3/22/2018 1:30 PM
15	To me, PM refers to individuals with no functional enzyme.	3/21/2018 10:15 AM
16	Classifying IM/PM as PM was superior compared to its classification as IM, in terms of explained variability of endoxifen PK by CYP2D6 (Schroth et al Frontiers in Pharmacology 2017)	3/21/2018 5:54 AM
17	from a safety perspective, this is preferable however, this probably deserves its own subcategory (e.g., PM+)	3/20/2018 4:28 PM
18	I like PM being only AS=0. Otherwise it will be very difficult to remember where the cutoffs are.	3/20/2018 9:26 AM
19	The Phenotype is closest to PM/PM	3/19/2018 7:31 PM
20	*4 and *5 are no functional genes; *10 is reduced function, so combining these its preferable to err on the PM, otherwise we end up with ridiculous fractions.	3/19/2018 4:26 PM
21	I am an implemented and have categorized such patients as CYP2D6 IMs. To the best of my knowledge, there have been therapeutic failures in this group of patients when we prescribed medications that are affected by CYP2D6 polymorphism.	3/19/2018 2:06 PM

Q2 Do you think an AS of 2.25 should be grouped as an UM or NM? Example includes: CYP2D6*1xN/*10.

Answered: 25 Skipped: 0



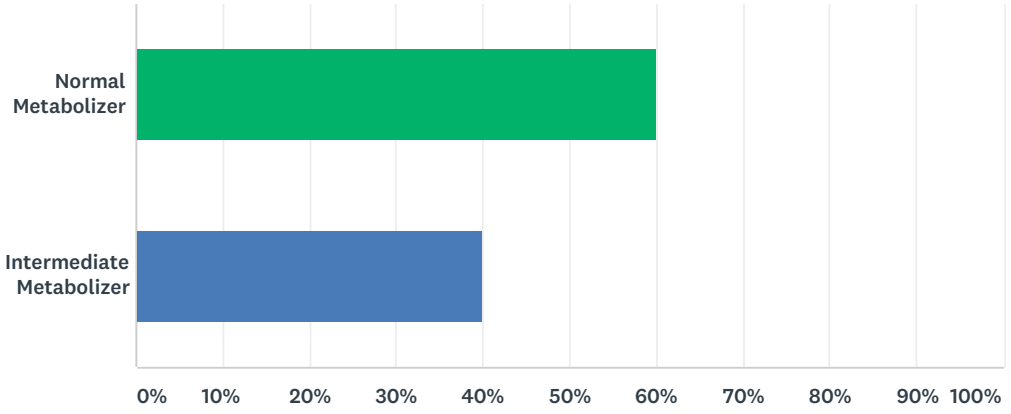
ANSWER CHOICES	RESPONSES	
Ultrarapid Metabolizer	52.00%	13
Normal Metabolizer	48.00%	12
TOTAL		25

#	WHY DO YOU THINK THE OPTION YOU CHOSE IS PREFERABLE?	DATE
1	The result of the test will be: 3 copies of the CYP2D6 allele. It is possible that the *10 allele is duplicated. AS is most likely to be similar to 1.5; the dosing advice for NM will be more appropriate than the dosing advice for UM.	4/2/2018 4:30 PM
2	We previously studied the relationship between copy number and tamoxifen efficacy, and observed no significant association.	3/31/2018 11:16 PM
3	If the AS of 0.25 is categorized as IM, the interval of IM should range from 0.25 to 1 and the interval of NM should range from 1.25 to 2	3/30/2018 10:25 AM
4	More than 2.0 fully functional alleles should be considered UMs. As evidenced by the almost double AUC demonstrated by: J Clin Pharmacol. 2012 Mar;52(3):388-403. doi: 10.1177/0091270011398657. Epub 2011 May 4. Pharmacokinetics, safety, and tolerability of atomoxetine and effect of CYP2D6*10/*10 genotype in healthy Japanese men. Matsui A1, Azuma J, Witcher JW, Long AJ, Sauer JM, Smith BP, DeSante KA, Read HA, Takahashi M, Nakano M.	3/29/2018 3:47 PM
5	Effect of *10 will be negligible compared with two *1 alleles. 2.25 is closer to 2.	3/28/2018 12:41 PM
6	Ideally again a "rapid metabolizer" group for predicting activity (comparable to CYP2C19) would be great, so as to provide a better reflection of the likely phenotype, and avoid confusion when providing recommendations across different groups.	3/27/2018 8:27 PM
7	I don't agree with either but I cannot get through the question unless I pick one. This is a rapid. What is happening here is that you are ignoring recent publications. See: Caudle KE: Genetics in Medicine 19(2):215-223, 2017.	3/27/2018 10:29 AM
8	Not enough (significant) difference with NM group	3/27/2018 12:42 AM
9	given the severly reduced activity of *10 grouping these as NM seems more appropriate. To my knowledge, there is little data supporting grouping them either way	3/26/2018 7:17 PM
10	I think this is slightly more than normal. We haven't traditionally used Rapid Metabolizer for 2D6. It might be a consideration.	3/22/2018 1:31 PM
11	This is greater activity than *1/*1, so therefore consider it a UM.	3/21/2018 10:16 AM

12	Ultrarapid metabolizers should be exclusively EMxN/EM, given that only a fraction of UM phenotype is explained by gene duplication, i.e. specificity should be kept high. Secondly, solid data of EMxN/IM translated to phenotype are rarely available given the low incidence of this genotype.	3/21/2018 6:01 AM
13	this is a trivial difference, and a rare subgroup	3/20/2018 4:28 PM
14	Anything >2 should be UM, for simplicity of remembering cutoffs.	3/20/2018 9:26 AM
15	*1xN - depends on the value of N. But I prefer clean single digits	3/19/2018 4:27 PM

Q3 Do you think an AS of 1.25 should be grouped as a NM or IM? Examples include: CYP2D6 *1/*10; *2/*10.

Answered: 25 Skipped: 0



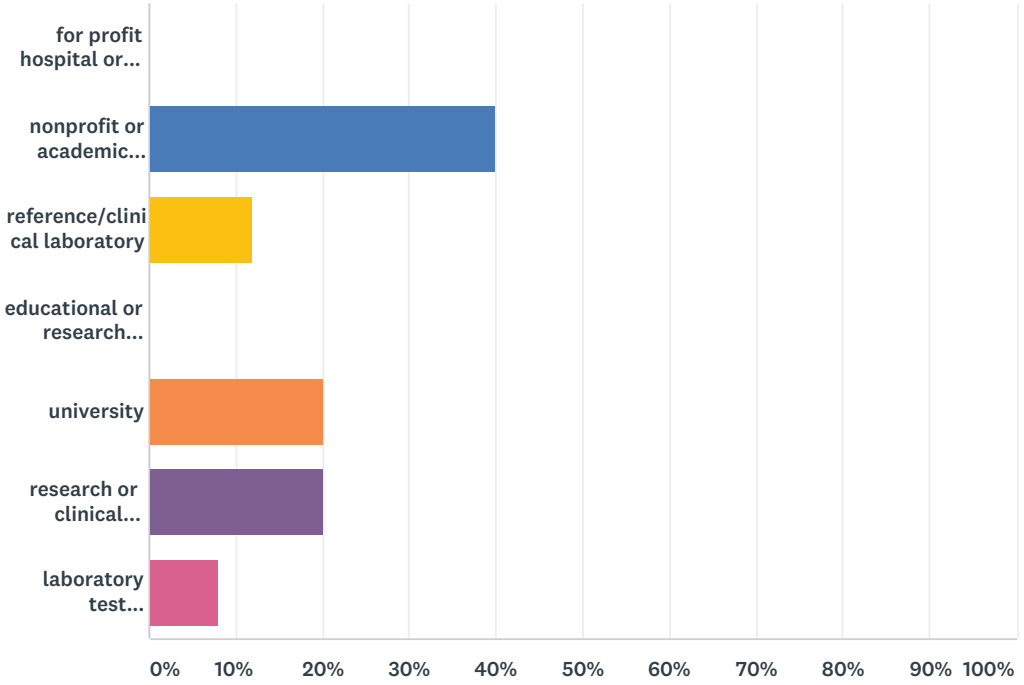
ANSWER CHOICES	RESPONSES	
Normal Metabolizer	60.00%	15
Intermediate Metabolizer	40.00%	10
TOTAL		25

#	WHY DO YOU THINK THE OPTION YOU CHOSE IS PREFERABLE?	DATE
1	Even an As OF 1 might be considered an NM by some.	4/2/2018 7:25 AM
2	In our study using Asian population,we grouped CYP2D6*1/*10 as "IM" ,which was defined in our classification. We observed significantly differernt clinical response to tamoxifen among the *1/*1, *1(*2)/*10 or null , and *10 or null/*10 or null groups, although the definition of group is completely different from that used in this survey.	3/31/2018 11:16 PM
3	If the AS of 0.25 is categorized as IM, the interval of IM should range from 0.25 to 1 and the interval of NM should range from 1.25 to 2	3/30/2018 10:26 AM
4	These genotypes have very similar AUCs compared to *1/*1 and *1/*2.	3/29/2018 3:54 PM
5	Intermediate should have at least one loss of function allele. *10 only decreases function even if this is of some significance. Best to keep IM definition between 0.25 and 1 in my view so that this category has clear meaning.	3/28/2018 12:46 PM
6	Although evidence indicates that *1/*10 and *1/*1 do not exhibit significantly different PK parameters in vivo for tramadol and tamoxifen, it seems that *1/*10 may yield a different phenotype than *1/*1 for some substrates (Kim 2018; Wu 2014), which may prompt, for some substrates, for different recommendations. Again from an implementer's perspective, it is easier for a clinician who is not used to PGx to understand that there could be the same recommendation for two different phenotypes, rather than understand that there could be two different recommendations for the same phenotype name (as for DPYD, which is highly confusing to our providers).	3/27/2018 8:47 PM
7	Tricky one... I am doubting. Would need to check the available evidence again where this group would end up. Based on where the *10 is coming from (AS 0.5) and my recollection of the evidence, I would choose now for NM...	3/27/2018 12:45 AM
8	grouping as IM would lead to a wide range of activity making it difficult to see an effect of those with an AS of 0.25	3/26/2018 7:20 PM
9	I think this one is harder. I think that many *10 may have been *36 in the literature.	3/22/2018 1:34 PM

10	This is difficult, but based on PMID28512430 I would elect it to be NM.	3/21/2018 10:19 AM
11	Classifying EM/IM including EM/*10 as an EM phenotype was superior in explaining the variability of endoxifen PK, as compared to their classification as IM phenotype (Schroth et al Frontiers in Pharmacology, 2017)	3/21/2018 6:05 AM
12	I have seen no data to the contrary	3/20/2018 4:29 PM
13	I don't think this one matters since I'm expecting the treatment recommendations between IM and NM will be drug and AS specific. Might as well keep the AS boundaries as simple as possible.	3/20/2018 9:27 AM
14	Normal as the *1 & *1 will dominate.	3/19/2018 4:28 PM

Q4 Which of the following describes your workplace setting ?

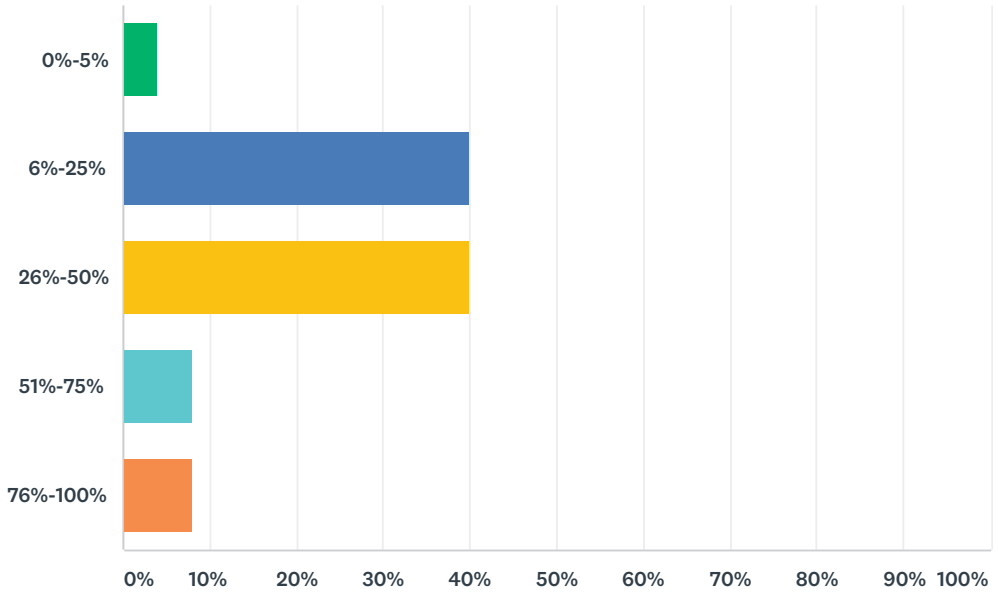
Answered: 25 Skipped: 0



ANSWER CHOICES	RESPONSES	
for profit hospital or clinic	0.00%	0
nonprofit or academic hospital or clinic	40.00%	10
reference/clinical laboratory	12.00%	3
educational or research resource	0.00%	0
university	20.00%	5
research or clinical institute	20.00%	5
laboratory test interpretation service	8.00%	2
TOTAL		25

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

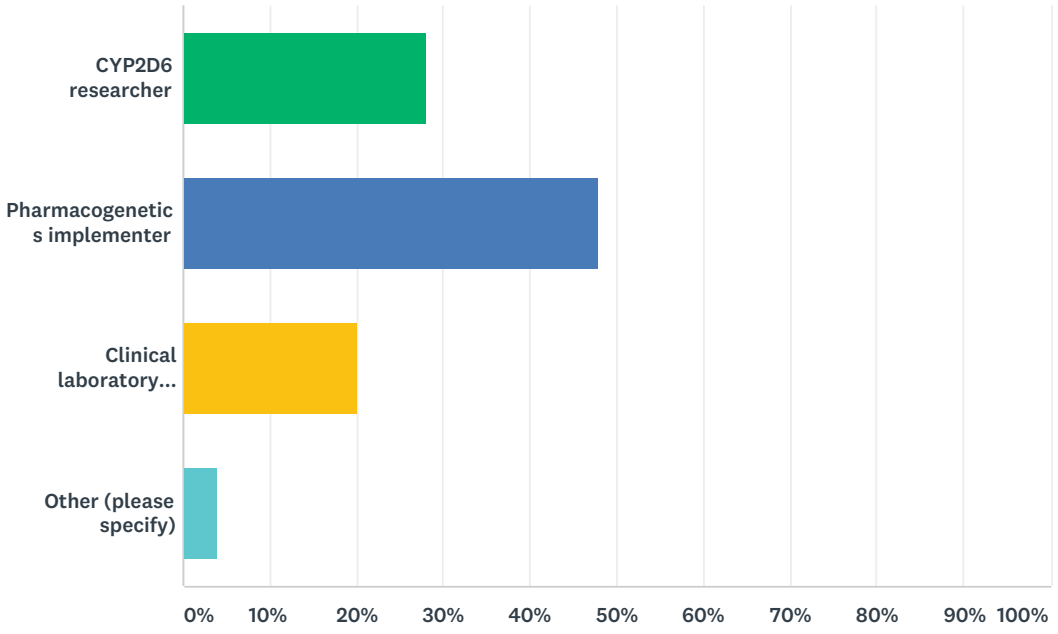
Answered: 25 Skipped: 0



ANSWER CHOICES	RESPONSES	
0%-5%	4.00%	1
6%-25%	40.00%	10
26%-50%	40.00%	10
51%-75%	8.00%	2
76%-100%	8.00%	2
TOTAL		25

Q6 Which of the following best describes your primary job?

Answered: 25 Skipped: 0



ANSWER CHOICES	RESPONSES	
CYP2D6 researcher	28.00%	7
Pharmacogenetics implementer	48.00%	12
Clinical laboratory professional	20.00%	5
Other (please specify)	4.00%	1
TOTAL		25

#	OTHER (PLEASE SPECIFY)	DATE
1	PGx Researcher	3/21/2018 11:21 AM