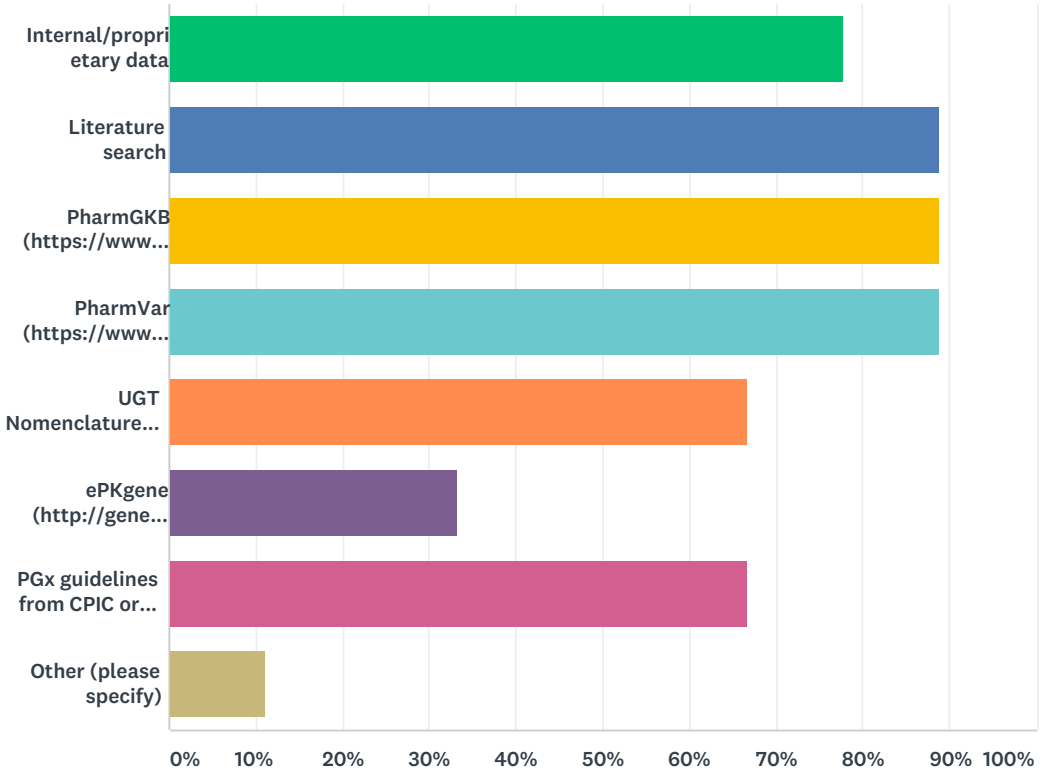
Q1 Please enter your unique individual Survey Monkey Code that wassent to you by Julian Arbuckle:

Answered: 7 Skipped: 2

#	RESPONSES	DATE
1	7507	11/5/2019 8:05 AM
2	2088	10/14/2019 8:53 PM
3	5351	10/11/2019 9:50 PM
4	3309	10/11/2019 1:58 PM
5	7755	10/11/2019 8:07 AM
6	7345	10/1/2019 3:22 PM
7	1744	9/25/2019 3:07 AM

Q2 What sources of evidence do you use in assessing potential functional impact of known alleles in ADME genes? Select all that apply.

Answered: 9 Skipped: 0



ANSWER CHOICES	RESPONSES	
Internal/proprietary data	77.78%	7
Literature search	88.89%	8
PharmGKB (https://www.pharmgkb.org/)	88.89%	8
PharmVar (https://www.pharmvar.org/)	88.89%	8
UGT Nomenclature Site (https://www.pharmacogenomics.pha.ulaval.ca/ugt-alleles-nomenclature/)	66.67%	6
ePKgene (http://gene.druginteractioninfo.org/)	33.33%	3
PGx guidelines from CPIC or DPWG	66.67%	6
Other (please specify)	11.11%	1
Total Respondents: 9		

#	OTHER (PLEASE SPECIFY)	DATE
1	UW DDI https://www.druginteractioninfo.org/	9/26/2019 5:30 PM

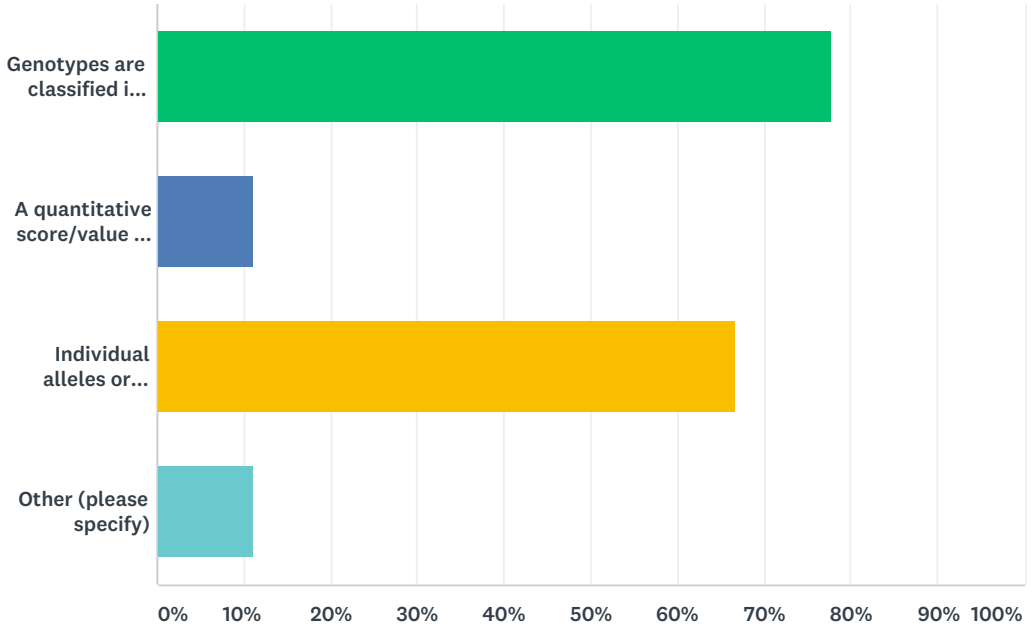
Q3 If you use existing databases in assessing ADME variant functionality, what, if any, are the major gaps in existing resources for your purposes? Please describe:

Answered: 8 Skipped: 1

#	RESPONSES	DATE
1	transporter mediated disposition	11/5/2019 8:05 AM
2	. There are harmonized criteria among all the sources/databases in defining clinical relevance of a ADME variant. . For transporter variants, often there is no transporter protein data or characterization of the system scaling factors to allow comparison of publications across different laboratories.	10/14/2019 8:53 PM
3	Lack of well annotated databases, particularly for less well characterized genes – certain genes have been covered well, but for the majority there is limited curated information, particularly summarizing what is known about clinical impact.	10/11/2019 9:50 PM
4	range of ethnicity and impact	10/11/2019 1:58 PM
5	----	10/11/2019 8:07 AM
6	NA	10/1/2019 3:22 PM
7	Lack of transporter database.	9/26/2019 5:30 PM
8	Testing	9/16/2019 11:29 PM

Q4 How does your company model ADME genetic variation in statistical analyses? Select all that apply:

Answered: 9 Skipped: 0



ANSWER CHOICES	RESPONSES	
Genotypes are classified into phenotypes (e.g. Extensive function, intermediate function, poor Function)	77.78%	7
A quantitative score/value is calculated per individual representing predicted ADME gene functionality	11.11%	1
Individual alleles or variants are tested	66.67%	6
Other (please specify)	11.11%	1
Total Respondents: 9		

#	OTHER (PLEASE SPECIFY)	DATE
1	Not relevant to role	10/1/2019 3:22 PM

Q5 As a follow-up to Question 4 if multiple approaches are used for modelling ADME genetic variation in statistical analyses please describe further scenarios in which each approach is applied:

Answered: 7 Skipped: 2

#	RESPONSES	DATE
1	N/A	11/5/2019 8:05 AM
2	. Usually only one approach would be prespecified and used for a given compound; . Phenotype classification is usually used when a variety of genetic variants exist for a given gene with each variant having good understanding of functionality, such as CYP2D6. Otherwise, individual variants may be tested.	10/14/2019 8:53 PM
3	Depends on the specific gene of interest - for certain genes where there is enough information to assign phenotype to genotypes, phenotype (eg "poor metabolizer") is used in statistical models. Where sufficient information is not available or where there is interest in testing alleles separately, each allele is tested.	10/11/2019 9:50 PM
4	Approaches depend on which ADME genes are in question, clinically known/validate effect or whether the analysis in more exploratory research in nature	10/11/2019 8:07 AM
5	N	10/1/2019 3:22 PM
6	It just depends on whether this is a known way to call phenotype, if not, individual alleles are assessed as needed.	9/26/2019 5:30 PM
7	Testing	9/16/2019 11:29 PM

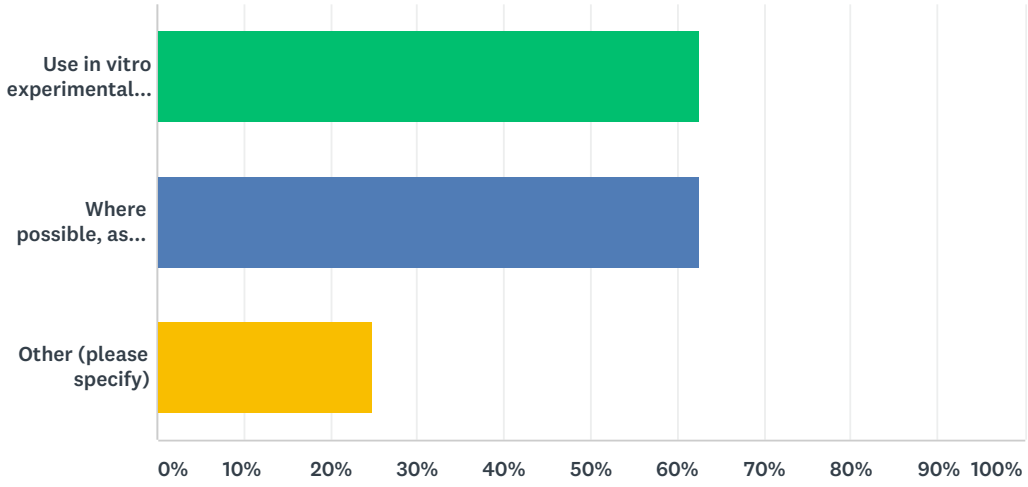
Q6 If you use phenotype annotations or quantitative scores as part of ADME PGx analyses, how are these defined? (Internal definition used, Definition from external source used) Please describe:

Answered: 7 Skipped: 2

#	RESPONSES	DATE
1	N/A	11/5/2019 8:05 AM
2	Both internal definition and external definition are integrated for use.	10/14/2019 8:53 PM
3	Generally use definitions provided by PharmGKB/CPIC.	10/11/2019 9:50 PM
4	internal	10/11/2019 1:58 PM
5	----------	10/11/2019 8:07 AM
6	External sources from list above using generally accepted nomenclature, no internal definitions are used.	9/26/2019 5:30 PM
7	Testing	9/16/2019 11:29 PM

Q7 It has been demonstrated that the predicted metabolic phenotype of some genetic variants may differ for different substrates. How do you asses the impact of such variants in clinical genetic analyses? Select all that apply:

Answered: 8 Skipped: 1

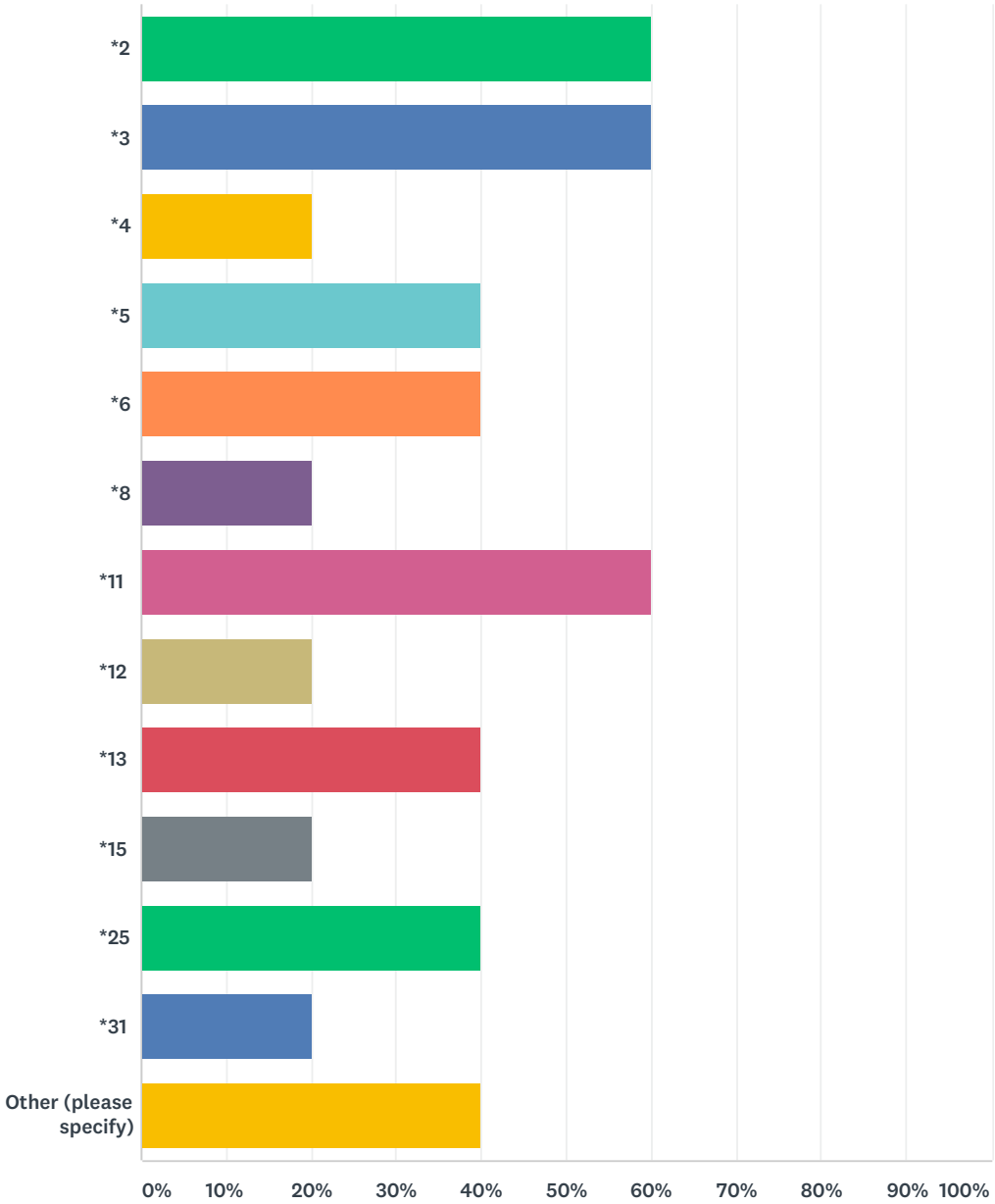


ANSWER CHOICES	RESPONSES	
Use in vitro experimental approaches to decipher the substrate-specific functionality and subsequently derive a predicted metabolic phenotype	62.50%	5
Where possible, asses impact of individual variants as a part of genetic analyses in human studies	62.50%	5
Other (please specify)	25.00%	2
Total Respondents: 8		

#	OTHER (PLEASE SPECIFY)	DATE
1	NA	10/11/2019 8:07 AM
2	No, we report generic prediction and communicate caveats to clinical teams.	9/26/2019 5:30 PM

Q8 Questions 8-15 are optional and please respond only if you are familiar with the genes and alleles listed. Which of the following CYP2C9 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?

Answered: 5 Skipped: 4



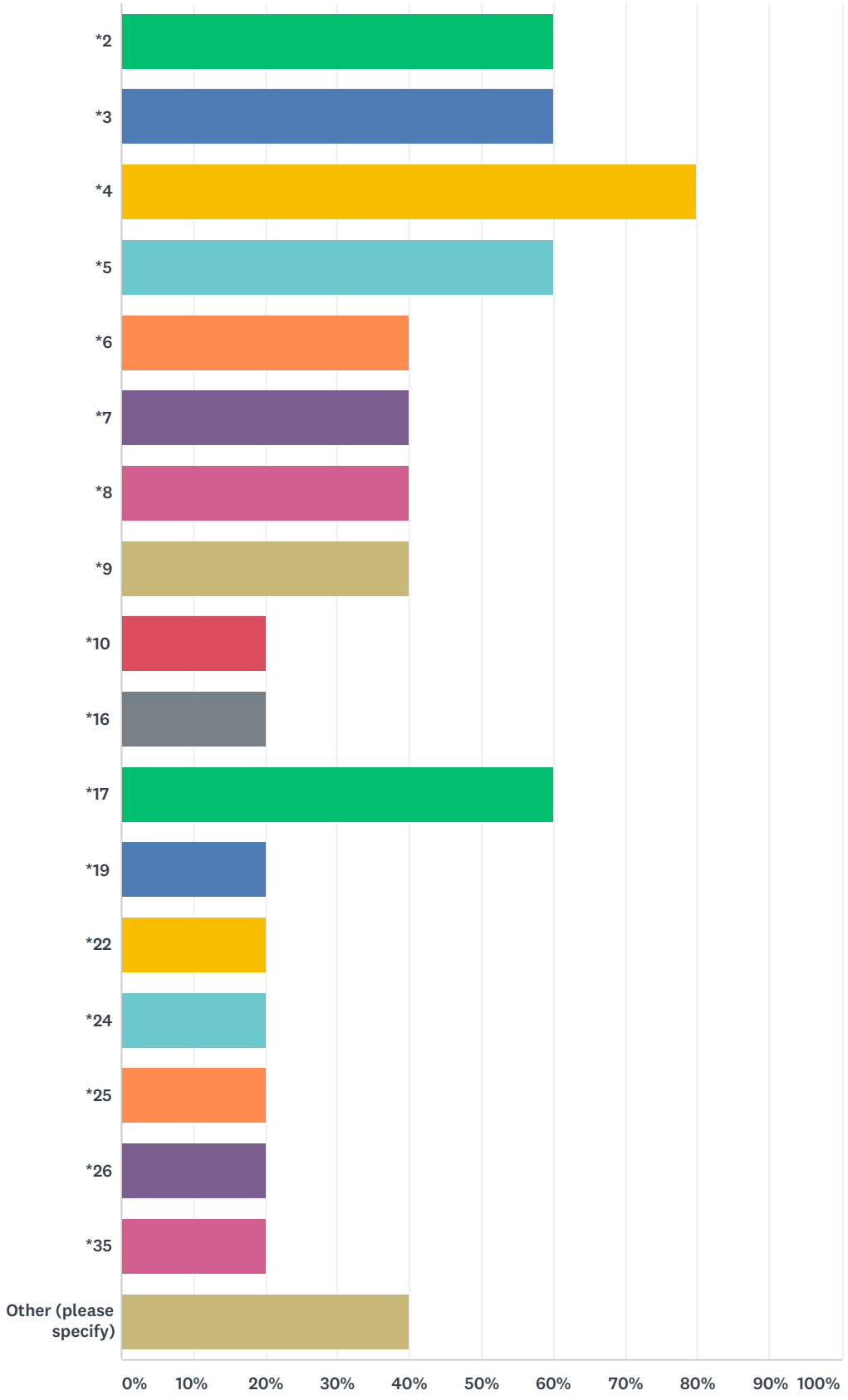
ANSWER CHOICES	RESPONSES	
*2	60.00%	3
*3	60.00%	3
*4	20.00%	1

*5	40.00%	2
*6	40.00%	2
*8	20.00%	1
*11	60.00%	3
*12	20.00%	1
*13	40.00%	2
*15	20.00%	1
*25	40.00%	2
*31	20.00%	1
Other (please specify)	40.00%	2
Total Respondents: 5		

#	OTHER (PLEASE SPECIFY)	DATE
1	N/A	11/5/2019 8:05 AM
2	We have looked at others, but given the frequency, *2 and *3 are routinely run.	9/26/2019 5:30 PM

Q9 Which of the following CYP2C19 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?

Answered: 5 Skipped: 4



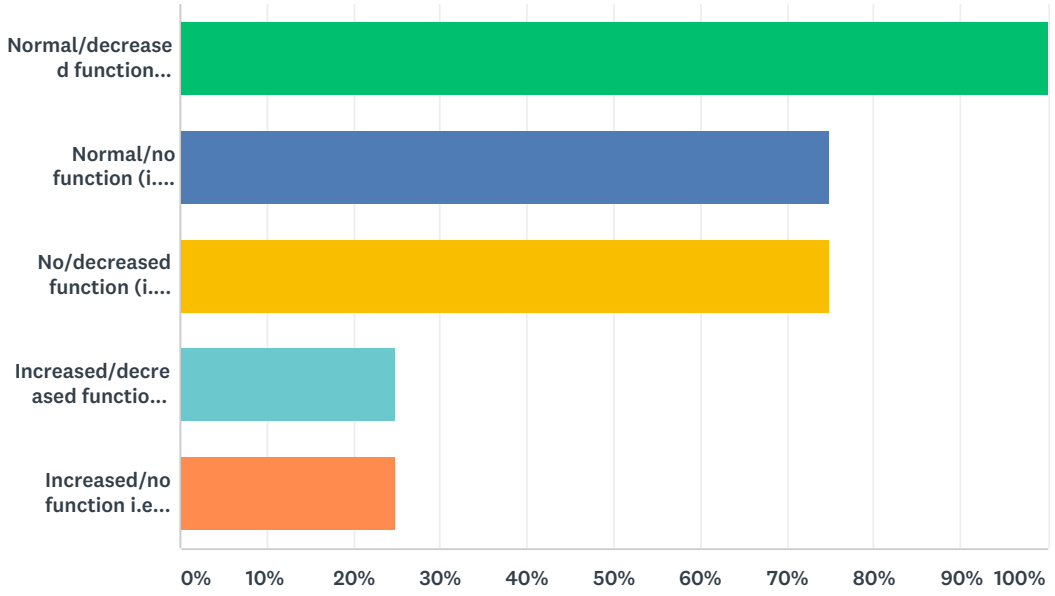
ANSWER CHOICES	RESPONSES	
*2	60.00%	3

*3	60.00%	3
*4	80.00%	4
*5	60.00%	3
*6	40.00%	2
*7	40.00%	2
*8	40.00%	2
*9	40.00%	2
*10	20.00%	1
*16	20.00%	1
*17	60.00%	3
*19	20.00%	1
*22	20.00%	1
*24	20.00%	1
*25	20.00%	1
*26	20.00%	1
*35	20.00%	1
Other (please specify)	40.00%	2
Total Respondents: 5		

#	OTHER (PLEASE SPECIFY)	DATE
1	N/A	11/5/2019 8:05 AM
2	Same caveat as above, have looked at others, but routinely do not run due to frequency.	9/26/2019 5:30 PM

Q10 Please select the CYP2D6 phenotype assignments based on allele functional status (diplotypes) below you agree with. Select all that apply:

Answered: 4 Skipped: 5



ANSWER CHOICES	RESPONSES	
Normal/decreased function (i.e. *1/*10) is EM	100.00%	4
Normal/no function (i.e. *1/*4) is IM	75.00%	3
No/decreased function (i.e. *4/*41) is IM	75.00%	3
Increased/decreased function (i.e. *1xN/*17) is EM	25.00%	1
Increased/no function i.e. (*1xN/*4) is IM	25.00%	1
Total Respondents: 4		

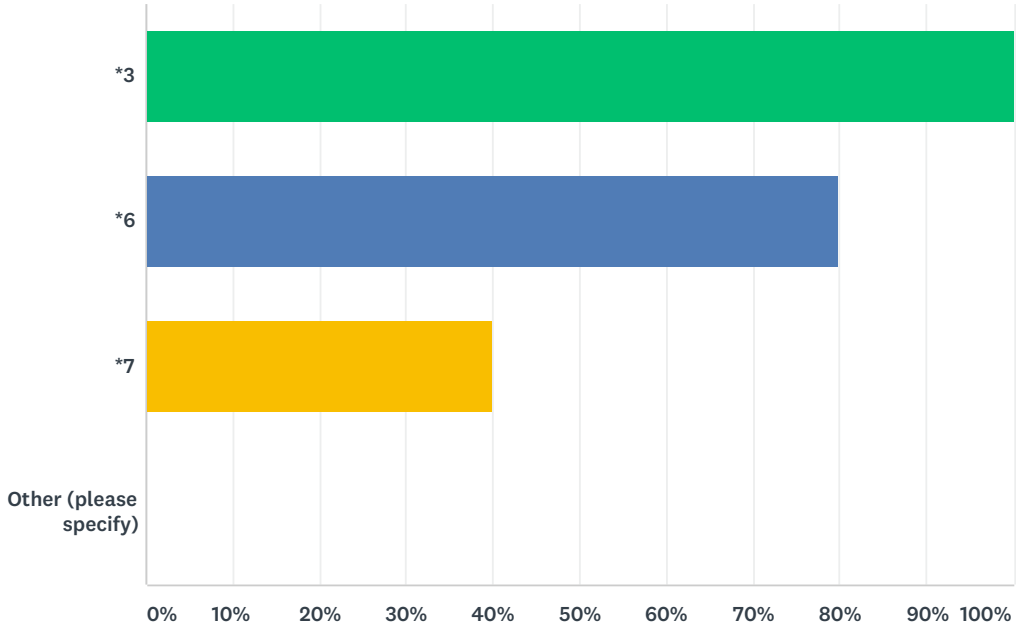
Q11 If you did not agree with any of the assignments in Question 10, please describe why:

Answered: 3 Skipped: 6

#	RESPONSES	DATE
1	N/A	11/5/2019 8:05 AM
2	We agree.	9/26/2019 5:30 PM
3	Testing	9/16/2019 11:29 PM

Q12 Which of the following CYP3A5 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?

Answered: 5 Skipped: 4

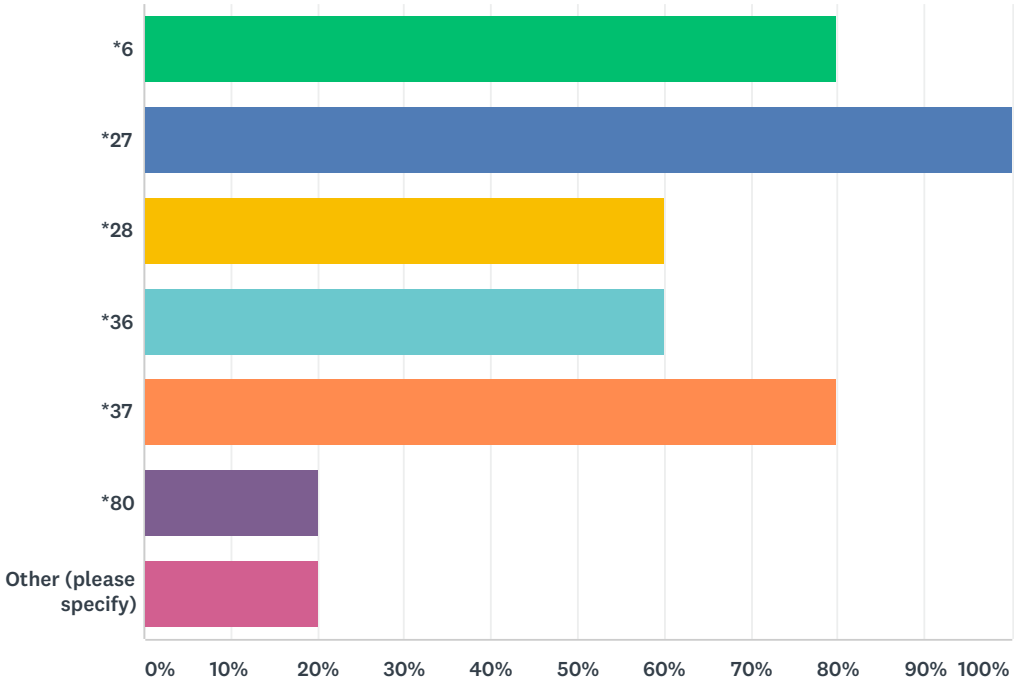


ANSWER CHOICES	RESPONSES	
*3	100.00%	5
*6	80.00%	4
*7	40.00%	2
Other (please specify)	0.00%	0
Total Respondents: 5		

#	OTHER (PLEASE SPECIFY)	DATE
	There are no responses.	

Q13 Which of the following UGT1A1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?

Answered: 5 Skipped: 4

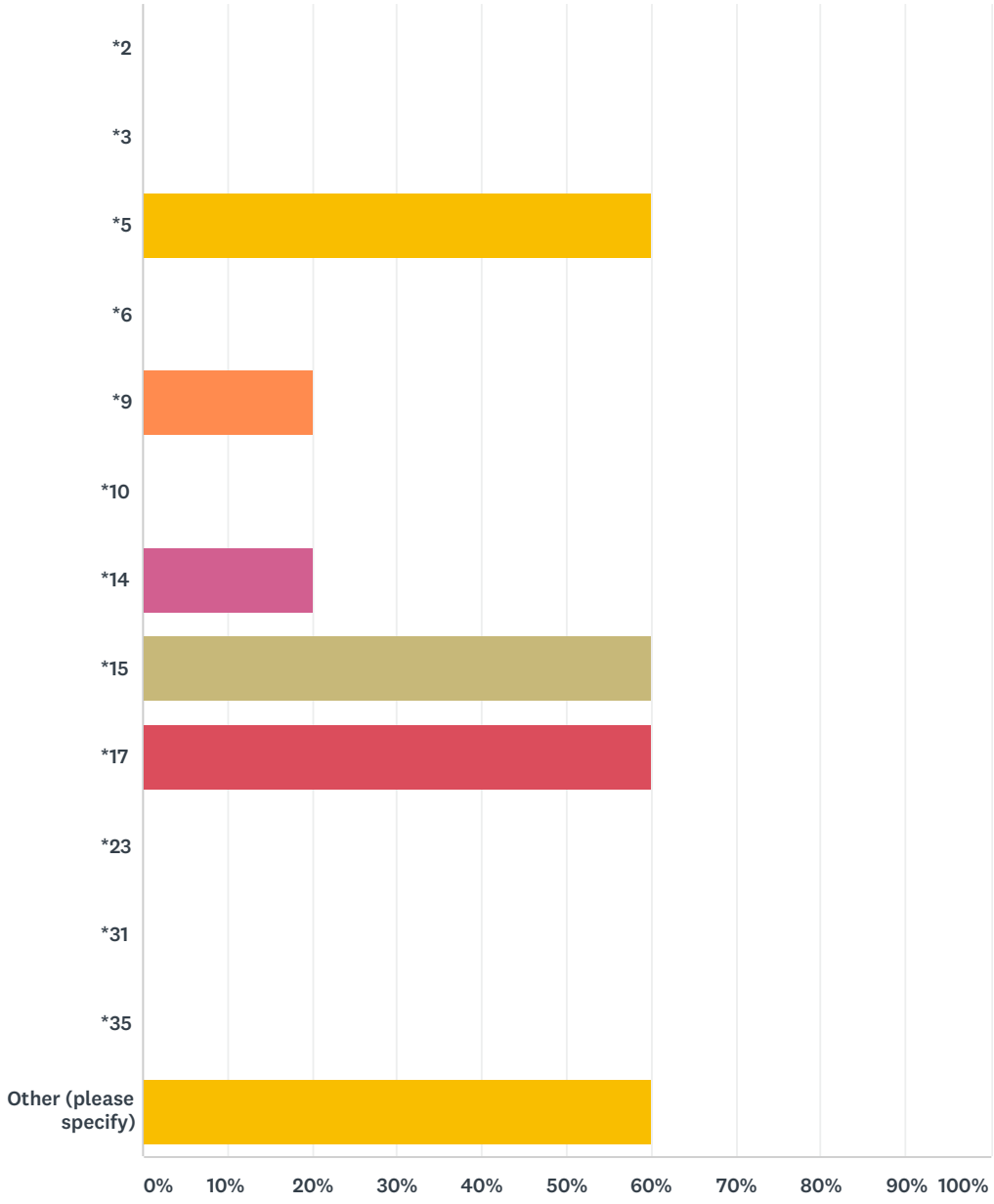


ANSWER CHOICES	RESPONSES	
*6	80.00%	4
*27	100.00%	5
*28	60.00%	3
*36	60.00%	3
*37	80.00%	4
*80	20.00%	1
Other (please specify)	20.00%	1
Total Respondents: 5		

#	OTHER (PLEASE SPECIFY)	DATE
1	We look at *60 routinely.	9/26/2019 5:30 PM

Q14 Which of the following SLCO1B1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?

Answered: 5 Skipped: 4



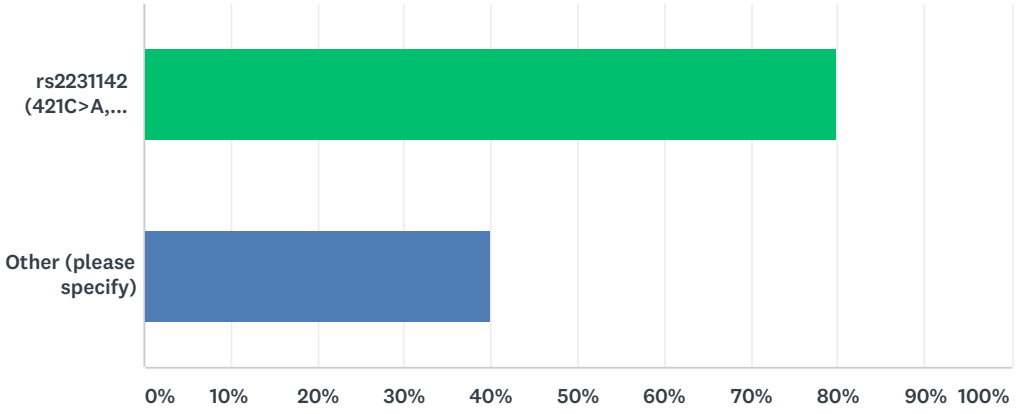
ANSWER CHOICES	RESPONSES	
*2	0.00%	0
*3	0.00%	0
*5	60.00%	3
*6	0.00%	0
*9	20.00%	1

*10	0.00%	0
*14	20.00%	1
*15	60.00%	3
*17	60.00%	3
*23	0.00%	0
*31	0.00%	0
*35	0.00%	0
Other (please specify)	60.00%	3
Total Respondents: 5		

#	OTHER (PLEASE SPECIFY)	DATE
1	N/A	11/5/2019 8:05 AM
2	*4 and *21	10/14/2019 8:53 PM
3	*1B routinely	9/26/2019 5:30 PM

Q15 Which of the following BCRP alleles do you consider to affect (increase or decrease) enzyme or transporter activity?

Answered: 5 Skipped: 4

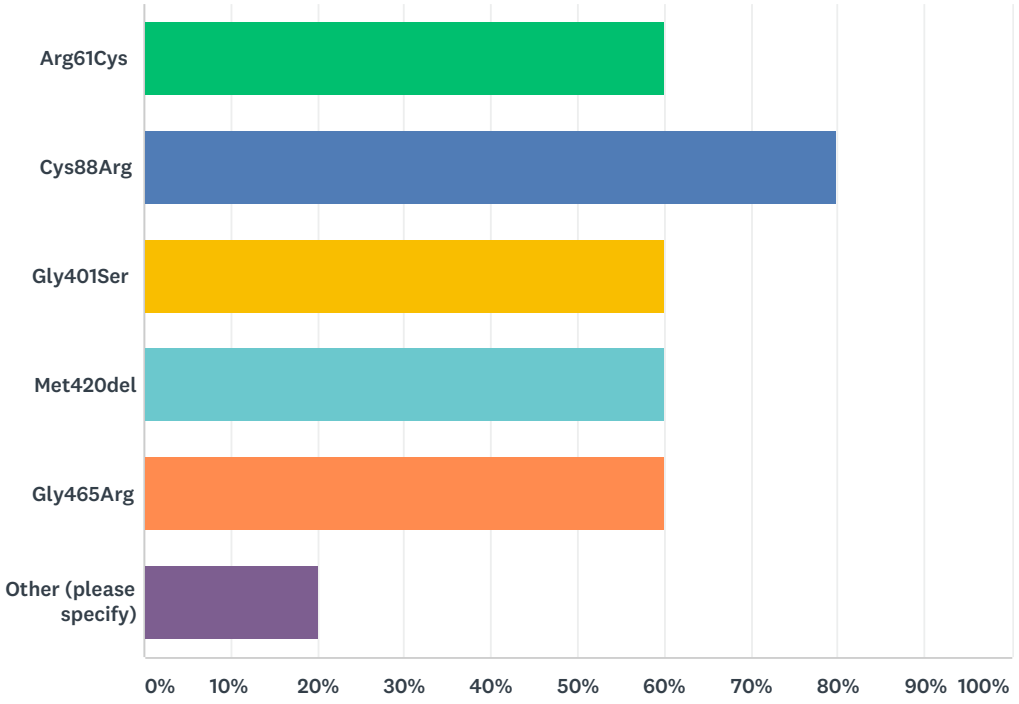


ANSWER CHOICES	RESPONSES	
rs2231142 (421C>A, Gln141Lys)	80.00%	4
Other (please specify)	40.00%	2
Total Respondents: 5		

#	OTHER (PLEASE SPECIFY)	DATE
1	N/A	11/5/2019 8:05 AM
2	rs72552713 routinely	9/26/2019 5:30 PM

Q16 Which of the following OCT1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?

Answered: 5 Skipped: 4

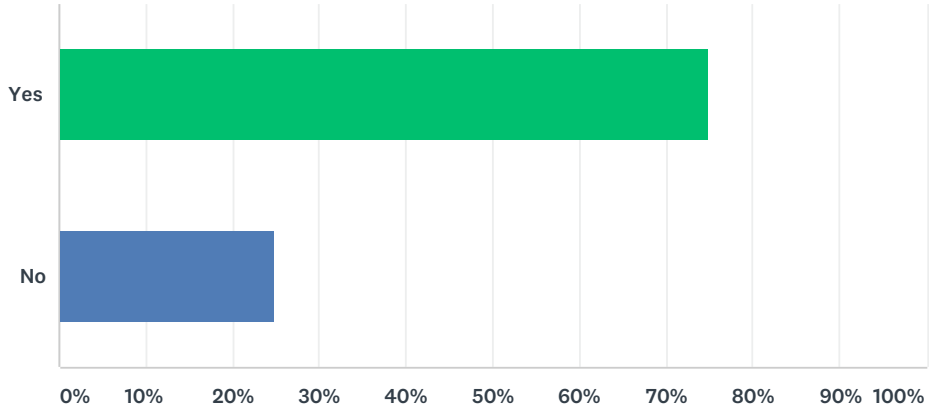


ANSWER CHOICES	RESPONSES	
Arg61Cys	60.00%	3
Cys88Arg	80.00%	4
Gly401Ser	60.00%	3
Met420del	60.00%	3
Gly465Arg	60.00%	3
Other (please specify)	20.00%	1
Total Respondents: 5		

#	OTHER (PLEASE SPECIFY)	DATE
1	N/A	11/5/2019 8:05 AM

Q17 Do you believe design of a standard ADME PGx Reference Set as described above would be valuable for the field?

Answered: 8 Skipped: 1



ANSWER CHOICES	RESPONSES	
Yes	75.00%	6
No	25.00%	2
TOTAL		8

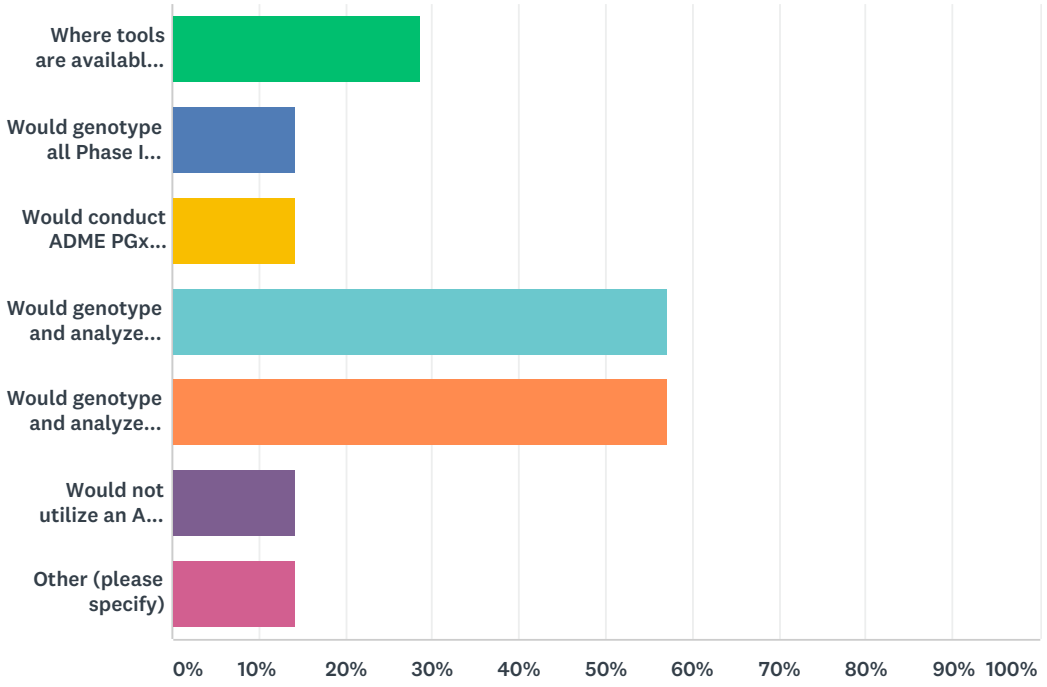
Q18 Please provide an explanation to for your response to Question 15:

Answered: 5 Skipped: 4

#	RESPONSES	DATE
1	Would allow to interprete the disposition profilie with variants relating to PG	11/5/2019 8:05 AM
2	There have been elegant publications that define clinically important ADME gene variants to genotype in clinical studies including CYPs, most UGTs, SLCO1B1, ABCG2 and OCT1. There is no need to duplicate efforts.	10/14/2019 8:53 PM
3	Useful in theory, but will be difficult to implement and substantial overlap with existing resources.	10/11/2019 9:50 PM
4	Standardization across industry with a specified panel would create the opportunity to grow the PGx field as is relates to clinical outcomes, ensure companies are aligned on strategy, and provide context for building a larger set that is more up to date.	9/26/2019 5:30 PM
5	Testing	9/16/2019 11:29 PM

Q19 Under what circumstances would you utilize an ADME PGx Reference Set at your company: Select all that apply

Answered: 7 Skipped: 2

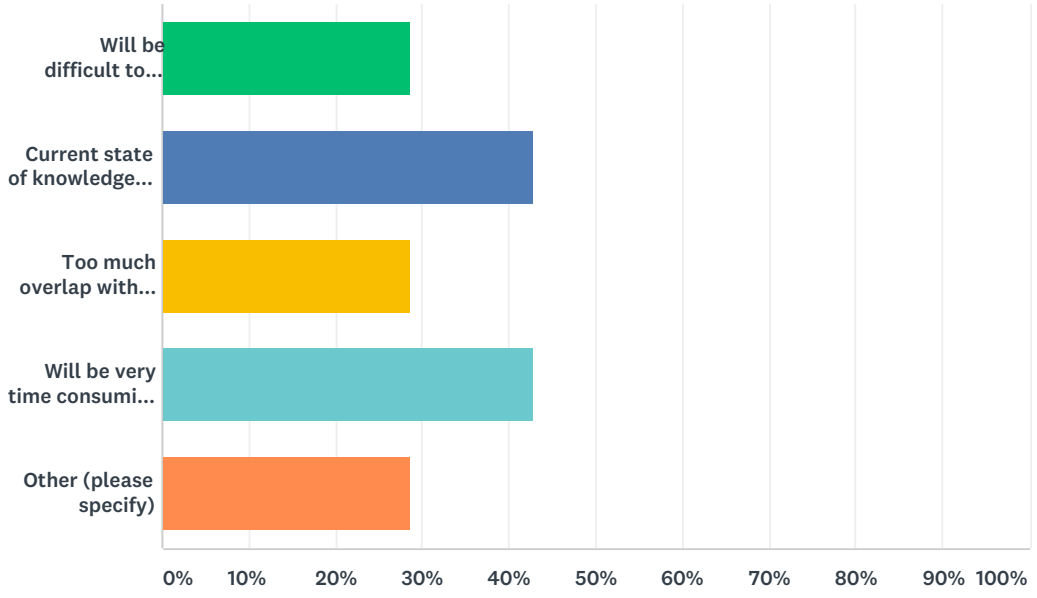


ANSWER CHOICES	RESPONSES	
Where tools are available, would use reference set to guide preclinical work	28.57%	2
Would genotype all Phase I clinical study subjects for alleles included in this set	14.29%	1
Would conduct ADME PGx analyses for all alleles in the set in all phase I studies	14.29%	1
Would genotype and analyze data for alleles in panel where there is some evidence from preclinical studies for involvement of the gene in disposition of a compound	57.14%	4
Would genotype and analyze data for genes in panel where there is unexplained PK variability	57.14%	4
Would not utilize an ADME PGx Reference set	14.29%	1
Other (please specify)	14.29%	1
Total Respondents: 7		

#	OTHER (PLEASE SPECIFY)	DATE
1	Would use to guide testing where inclusion or exclusion of subjects based on PGx genotype was required.	10/11/2019 9:50 PM

Q20 What possible challenges or limitations do you see in development or utility of an ADME Reference Set? Select all that apply:

Answered: 7 Skipped: 2

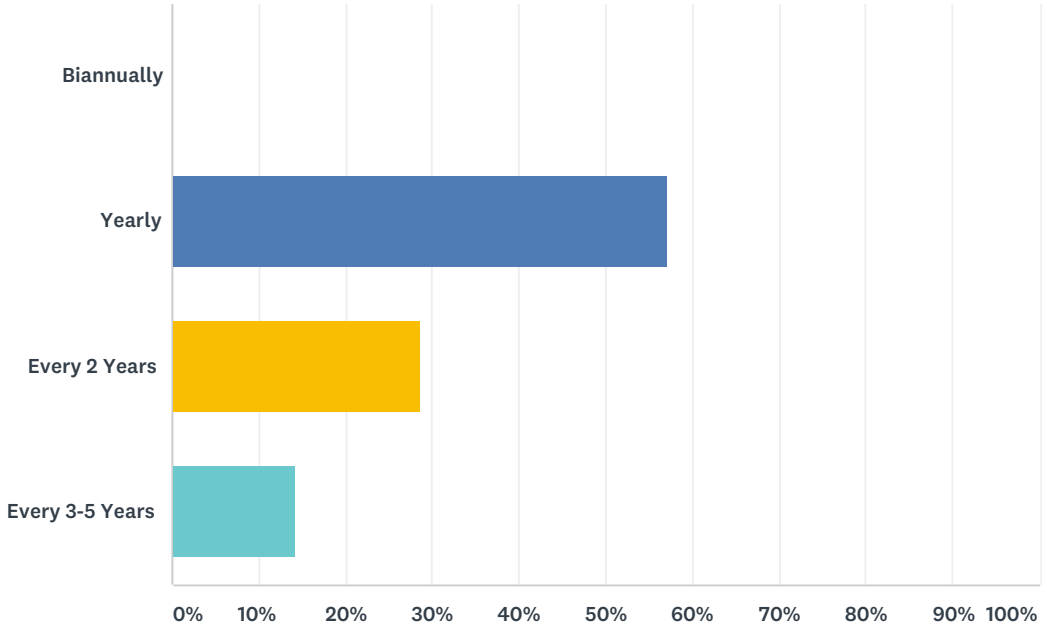


ANSWER CHOICES	RESPONSES	
Will be difficult to find agreement across the field	28.57%	2
Current state of knowledge is rapidly evolving – will be challenging to keep a reference set up to date	42.86%	3
Too much overlap with other existing resources	28.57%	2
Will be very time consuming to develop	42.86%	3
Other (please specify)	28.57%	2
Total Respondents: 7		

#	OTHER (PLEASE SPECIFY)	DATE
1	Acceptability by regulatory agencies when it comes to interpretation of NCE in submission dossier	11/5/2019 8:05 AM
2	Core panel would be easier to have agreement, it's more of the question around "non-core" or "new" alleles that could be difficult to agree on. Maybe a core and next level panel could provide flexibility. In that case, we don't believe that this would be hard to build or maintain if done in tiered way.	9/26/2019 5:30 PM

Q21 To be useful, how often would an ADME PGx Reference Set need to be updated?

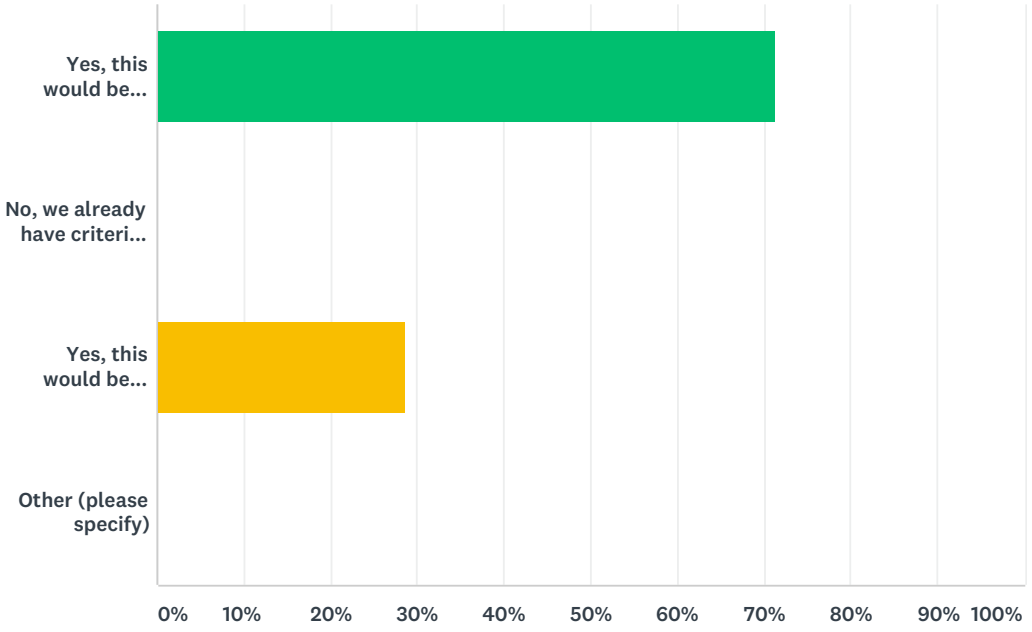
Answered: 7 Skipped: 2



ANSWER CHOICES	RESPONSES	
Biannually	0.00%	0
Yearly	57.14%	4
Every 2 Years	28.57%	2
Every 3-5 Years	14.29%	1
TOTAL		7

Q22 As an alternative to a defined reference set, do you see value in the creation of a recommended set of criteria to use for defining or identifying genetic variants with potential clinical relevance to be used in drug development?

Answered: 7 Skipped: 2



ANSWER CHOICES	RESPONSES	
Yes, this would be valuable	71.43%	5
No, we already have criteria we use that serve our needs	0.00%	0
Yes, this would be valuable, but in addition to a reference panel	28.57%	2
Other (please specify)	0.00%	0
TOTAL		7

#	OTHER (PLEASE SPECIFY)	DATE
	There are no responses.	

Q23 Please provide any additional comments on this topic:

Answered: 2 Skipped: 7

#	RESPONSES	DATE
1	A repository of observations about impact of alleles in ADME genes (similar to ClinVar) would be very useful for the field. This would allow pharma companies to share their knowledge/observations around variant functionality without requiring formal publication, and would be particularly valuable for rare variants.	10/11/2019 9:50 PM
2	With regard to question 21, if the panel is set up well to start, there won't be much new each year to add.	9/26/2019 5:30 PM