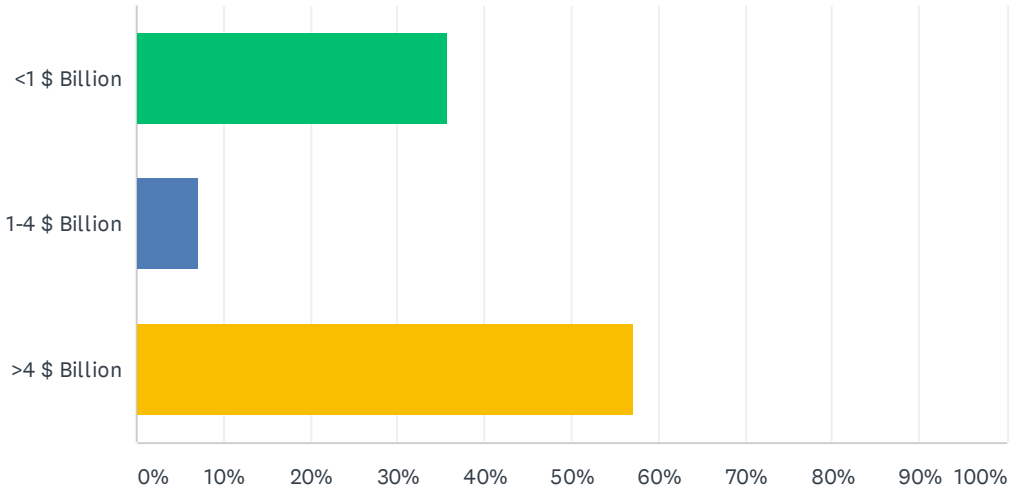
Q1 Please enter your unique individual Survey Monkey Code that was sent to you by Julian Arbuckle:

Answered: 9 Skipped: 6

#	RESPONSES	DATE
1	1744	11/5/2019 7:38 PM
2	5965	10/25/2019 2:27 PM
3	2088	10/14/2019 10:22 PM
4	4001	10/11/2019 10:19 PM
5	4099	10/11/2019 9:07 PM
6	7755	10/11/2019 11:25 AM
7	3078	10/10/2019 2:23 PM
8	We will not get 4M but Sam did not want us to remove anything either. He asked that we prioritize the most important items for the coming year (Keeping it at more like 2M or less)	10/9/2019 2:38 PM
9	5351	10/1/2019 6:35 PM

Q2 What were the pharmaceutical R&D expenses of your company in 2018?

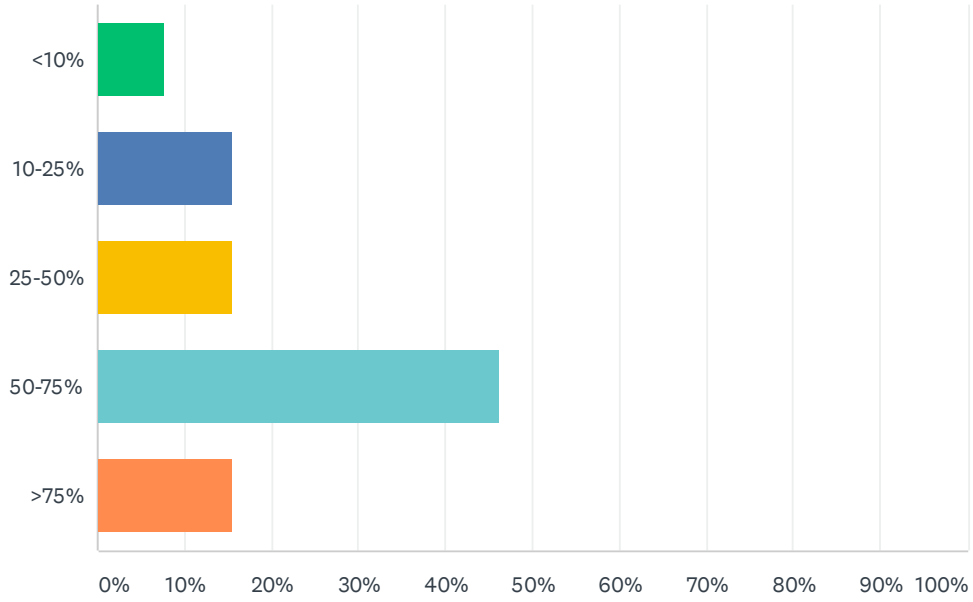
Answered: 14 Skipped: 1



ANSWER CHOICES	RESPONSES	
<1 $ Billion	35.71%	5
1-4 $ Billion	7.14%	1
>4 $ Billion	57.14%	8
TOTAL		14

Q3 What percentage of your pipeline is represented by small molecules:

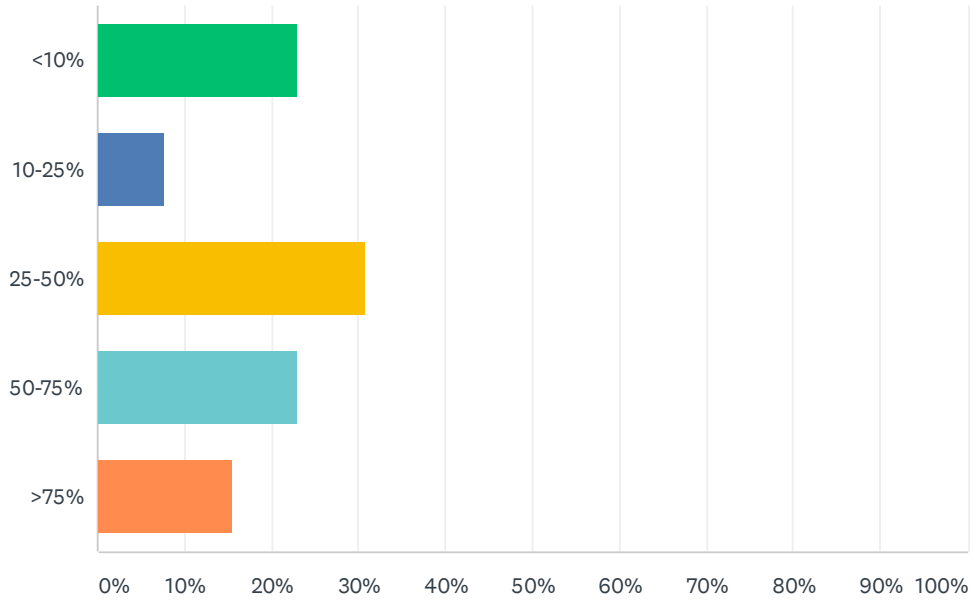
Answered: 13 Skipped: 2



ANSWER CHOICES	RESPONSES	
<10%	7.69%	1
10-25%	15.38%	2
25-50%	15.38%	2
50-75%	46.15%	6
>75%	15.38%	2
TOTAL		13

Q4 What percentage of your pipeline is represented by therapeutic proteins, vaccines, or other types of compounds (not small molecule):

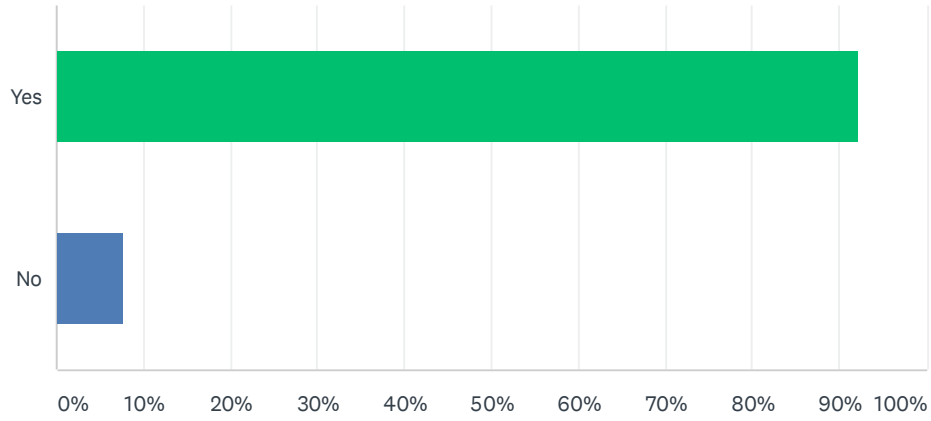
Answered: 13 Skipped: 2



ANSWER CHOICES	RESPONSES	
<10%	23.08%	3
10-25%	7.69%	1
25-50%	30.77%	4
50-75%	23.08%	3
>75%	15.38%	2
TOTAL		13

Q5 Do you typically conduct in vitro phenotyping studies to assess enzyme involvement in clearance of discovery or development compounds prior to phase 1 clinical studies?

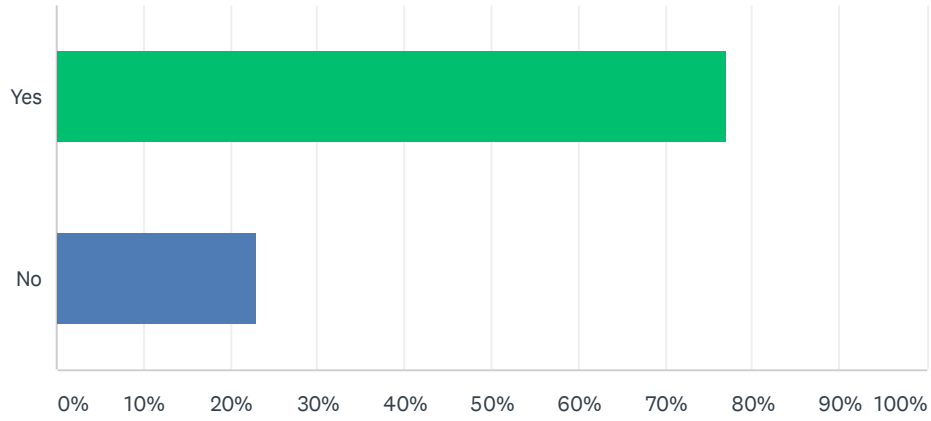
Answered: 13 Skipped: 2



ANSWER CHOICES	RESPONSES	
Yes	92.31%	12
No	7.69%	1
TOTAL		13

Q6 Do you typically conduct in vitro phenotyping studies to assess transporter involvement in clearance of discovery or development compounds prior to Phase 1 clinical studies?

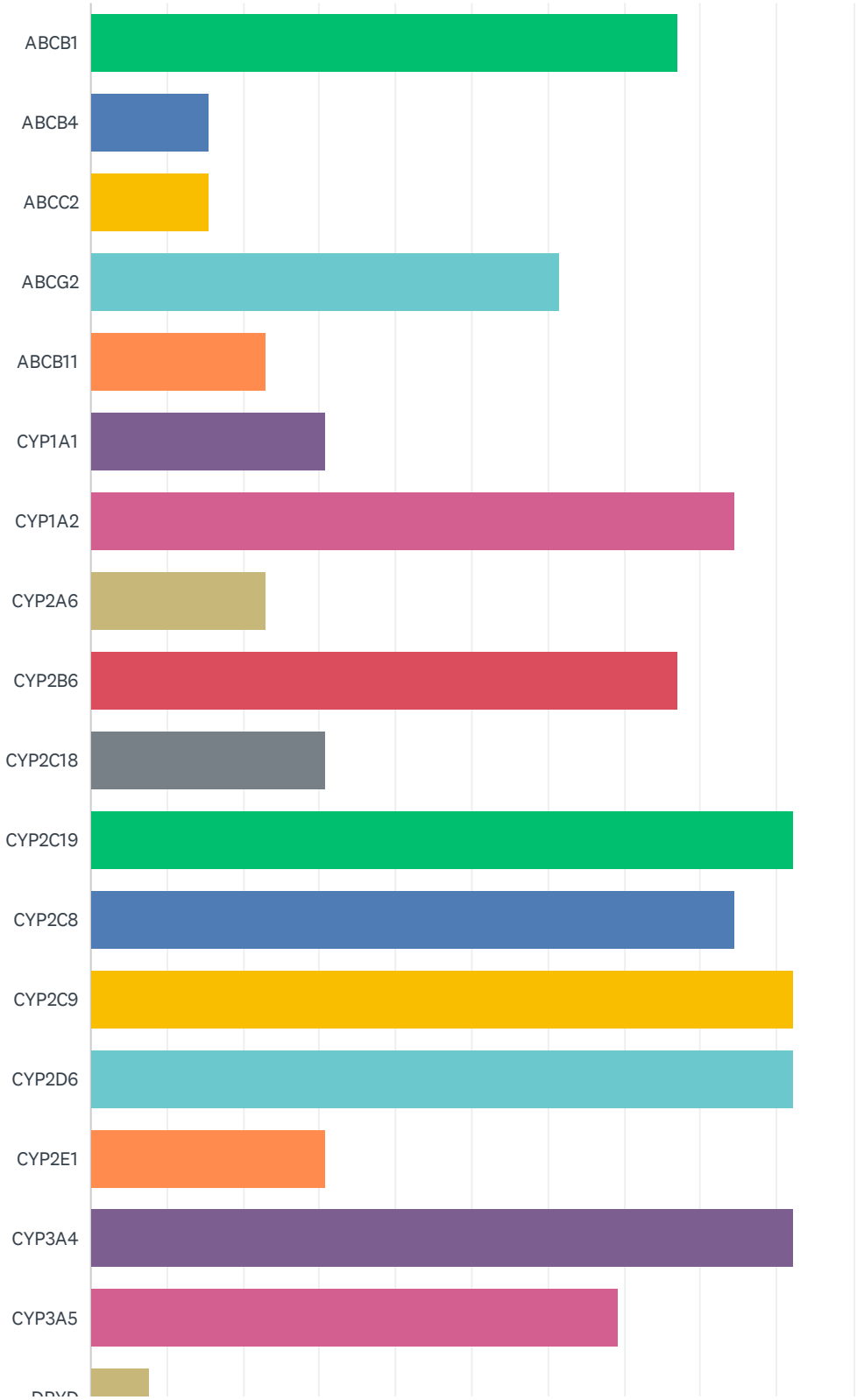
Answered: 13 Skipped: 2



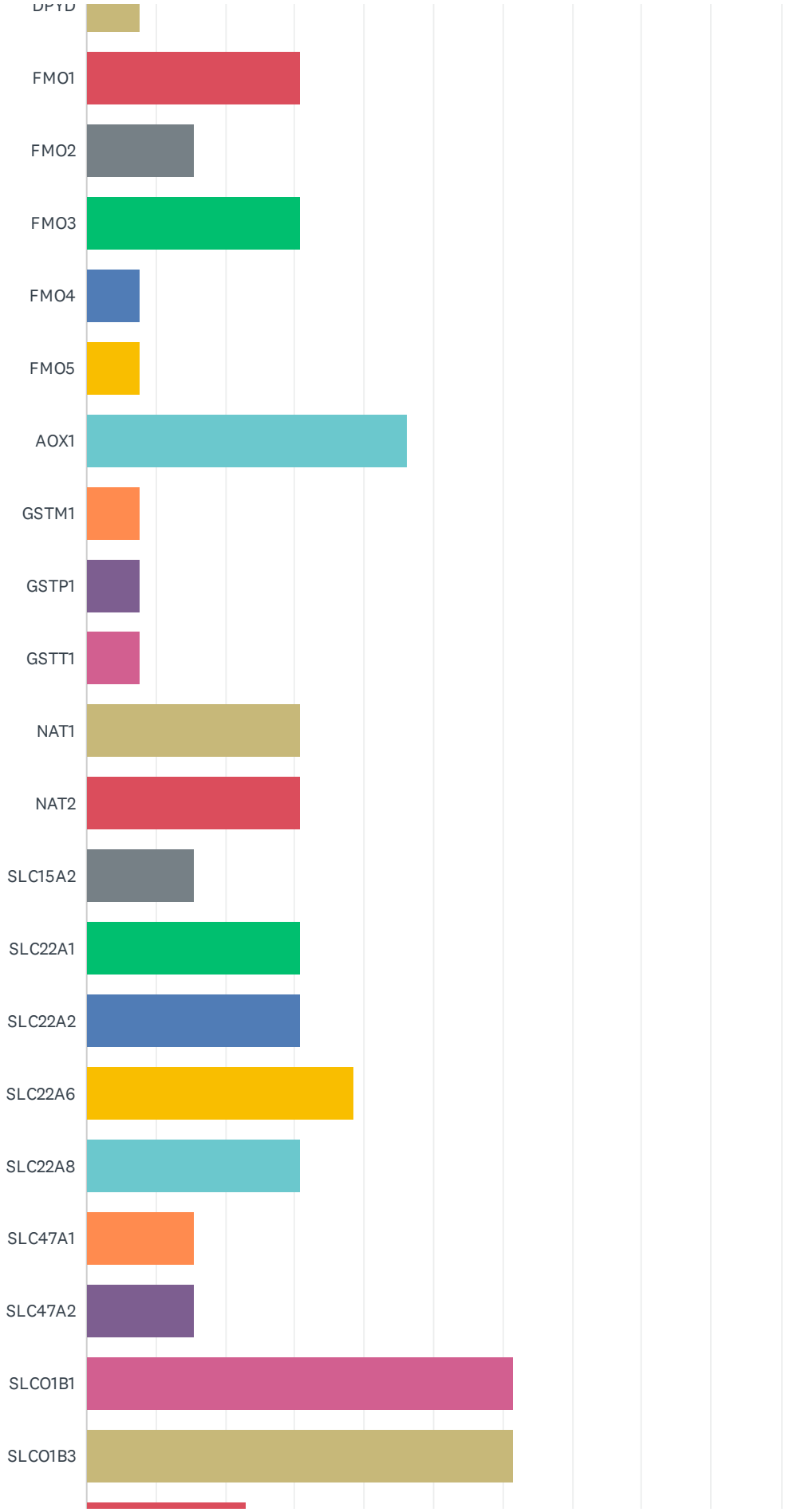
ANSWER CHOICES	RESPONSES	
Yes	76.92%	10
No	23.08%	3
TOTAL		13

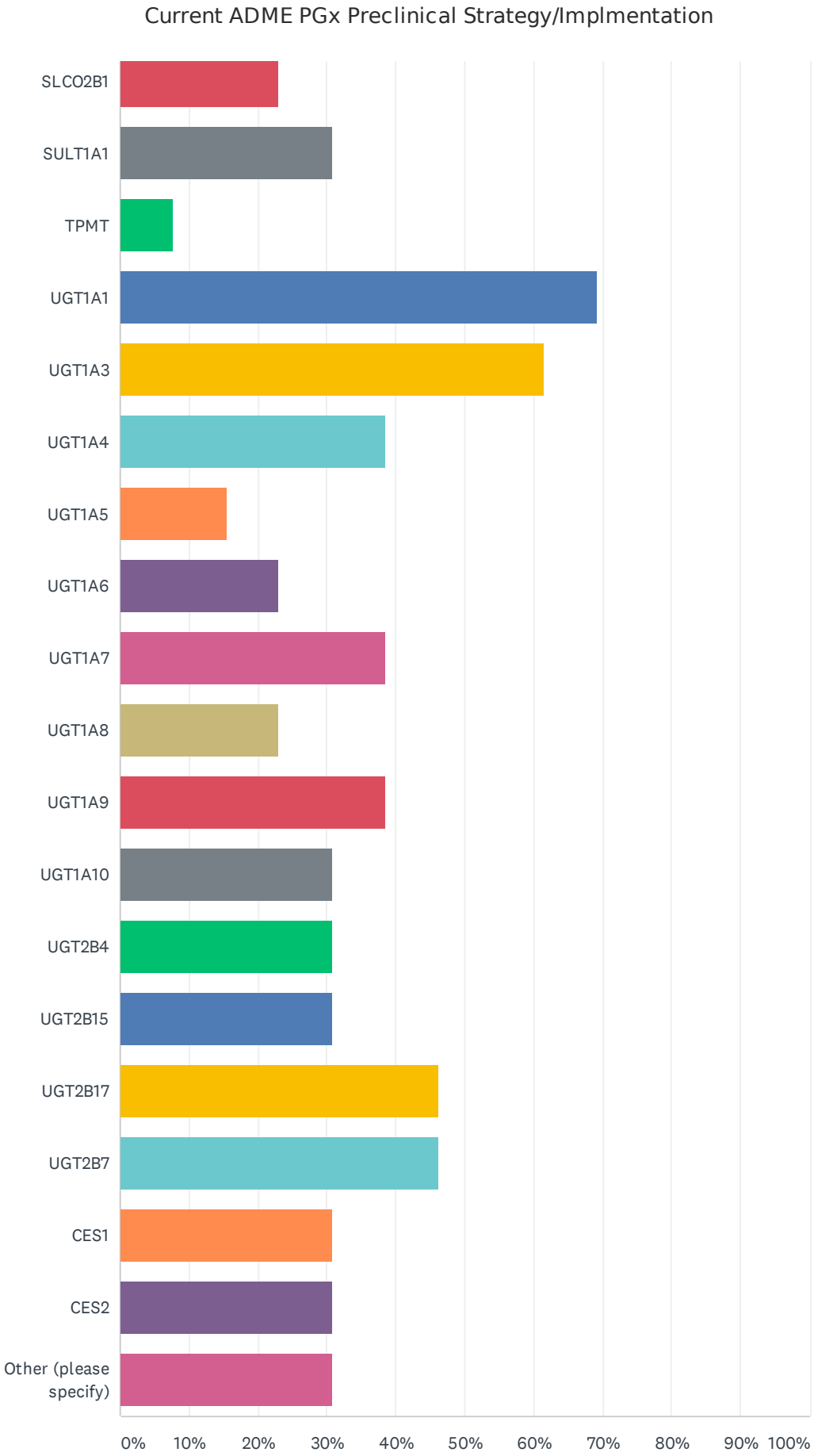
Q7 Which enzymes and transporters does your company test in vitro for their involvement in clearance of discovery or development compounds prior to phase 1 clinical studies? Select all that apply.

Answered: 13 Skipped: 2



Current ADME PGx Preclinical Strategy/Implmentation




Current ADME PGx Preclinical Strategy/Implmentation
SLCO2B1
SULT1A1
TPMT
UGT1A1
UGT1A3
UGT1A4
UGT1A5
UGT1A6
UGT1A7
UGT1A8
UGT1A9
UGT1A10
UGT2B4
UGT2B15
UGT2B17
UGT2B7
CES1
CES2
Other (please specify)
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

ANSWER CHOICES	RESPONSES	
ABCB1	76.92%	10
ABCB4	15.38%	2
ABCC2	15.38%	2
ABCG2	61.54%	8
ABCB11	23.08%	3
CYP1A1	30.77%	4
CYP1A2	84.62%	11
CYP2A6	23.08%	3
CYP2B6	76.92%	10
CYP2C18	30.77%	4
CYP2C19	92.31%	12
CYP2C8	84.62%	11
CYP2C9	92.31%	12
CYP2D6	92.31%	12
CYP2E1	30.77%	4
CYP3A4	92.31%	12
CYP3A5	69.23%	9
DPYD	7.69%	1
FMO1	30.77%	4
FMO2	15.38%	2
FMO3	30.77%	4
FMO4	7.69%	1
FMO5	7.69%	1
AOX1	46.15%	6
GSTM1	7.69%	1
GSTP1	7.69%	1
GSTT1	7.69%	1
NAT1	30.77%	4
NAT2	30.77%	4
SLC15A2	15.38%	2
SLC22A1	30.77%	4
SLC22A2	30.77%	4

SLC22A6	38.46%	5
SLC22A8	30.77%	4
SLC47A1	15.38%	2
SLC47A2	15.38%	2
SLCO1B1	61.54%	8
SLCO1B3	61.54%	8
SLCO2B1	23.08%	3
SULT1A1	30.77%	4
TPMT	7.69%	1
UGT1A1	69.23%	9
UGT1A3	61.54%	8
UGT1A4	38.46%	5
UGT1A5	15.38%	2
UGT1A6	23.08%	3
UGT1A7	38.46%	5
UGT1A8	23.08%	3
UGT1A9	38.46%	5
UGT1A10	30.77%	4
UGT2B4	30.77%	4
UGT2B15	30.77%	4
UGT2B17	46.15%	6
UGT2B7	46.15%	6
CES1	30.77%	4
CES2	30.77%	4
Other (please specify)	30.77%	4
Total Respondents: 13		

#	OTHER (PLEASE SPECIFY)	DATE
1	As required to understanding clearance mechanisms of NCE	2/25/2020 3:30 PM
2	CYP2J2	10/14/2019 10:22 PM
3	UGT2B10, MAOA, MAOB	10/11/2019 11:25 AM
4	nucleases, which is well understood already for the platform	10/3/2019 6:58 PM

Q8 Are there additional enzymes or transporters you would assess, given availability of appropriate and accurate in vitro tools? Please list.

Answered: 8 Skipped: 7

#	RESPONSES	DATE
1	No	2/27/2020 1:24 PM
2	THIS IS A TEST RESPONSE	1/23/2020 10:25 PM
3	Aldehyde oxidase beta-oxidation	11/5/2019 7:38 PM
4	no	10/25/2019 2:27 PM
5	• CYP1B1, CYP2J2, CYP3A7, CYP4A11 • AOX vs XO (xanthine oxidase) • EPHX1, EPHX2 • PON1, PON2, PON3 • SULT 1A2, 1A3, 1B1, 1E1, 2A1 • ADH, ALDH • UGT2A1, UGT2B10, UGT2B11, UGT2B28 • OAT2, SLC22A7	10/11/2019 10:19 PM
6	none	10/10/2019 2:23 PM
7	MDR1 and MRP2	10/9/2019 2:38 PM
8	No	10/3/2019 6:58 PM

Q9 What methods do you typically employ in preclinical studies to predict the fm (fraction metabolized) by particular enzymes? Please describe.

Answered: 12 Skipped: 3

#	RESPONSES	DATE
1	Utilization on selective inhibitors in rodents as well as knockout rodent models. For in vitro experiments, utilization of selective antibody inhibitors, chemical inhibitors, and/or RNAi in primary cell lines	2/25/2020 3:30 PM
2	Human hepatocytes with chemical inhibition (Azamulin & tienilic acid), human recombinant CYPs, human microsomes with chemical inhibition.	2/3/2020 4:14 PM
3	Radiolabeled ADME studies	1/30/2020 1:03 PM
4	ADME study	11/5/2019 7:38 PM
5	in vitro metabolism studies	10/25/2019 2:27 PM
6	. parent compound disappearance using recombinant human cytochrome P450s . human hepatocytes with and without ABT	10/14/2019 10:22 PM
7	Primary evaluations are done by evaluating potential for NCE to be metabolized by recombinant enzymes in conjunction with chemical inhibitors (where selective chemical inhibitors are available or characterized). • We are looking for agreement in methodology between recombinant enzymes and chemical inhibitor data. When no turnover (metabolite formation) is observed in recombinant enzymes, chemical inhibitor data are generally disregarded (potential for non-selective inhibition) • Scaling of metabolism using RAF or ISEF is considered with caution since overprediction of certain routes from recombinant enzymes may occur (eg CYP3A4) and more weight is placed on chemical inhibitor data. • In cases where metabolic CL fm estimations are less clear, additional approaches are employed such as (i) evaluation of metabolism in genotyped tissue fractions and/or (ii) a correlation analysis of metabolite formation in a range of individual human tissue donors with a large range in quantified protein of interest and/or catalytic activity. • For AO or GSTs, yardstick approach is used to estimate from in vitro.	10/11/2019 10:19 PM
8	measuring substrate loss in individual cDNA expressed P450s	10/11/2019 9:07 PM
9	Recombinant enzymes and hepatocytes with specific inhibitor followed by in vitro-in vivo scaling	10/11/2019 11:25 AM
10	Recombinant enzymes and ISEF approaches for CYPs, human liver microsomes with specific inhibitors and inhibitory antibodies are used as well	10/10/2019 2:23 PM
11	recombinant enzymes using the RAF method, inhibition with specific inhibitors in human hepatocytes or microsomes.	10/9/2019 2:38 PM
12	no applicable for RNA drugs	10/3/2019 6:58 PM

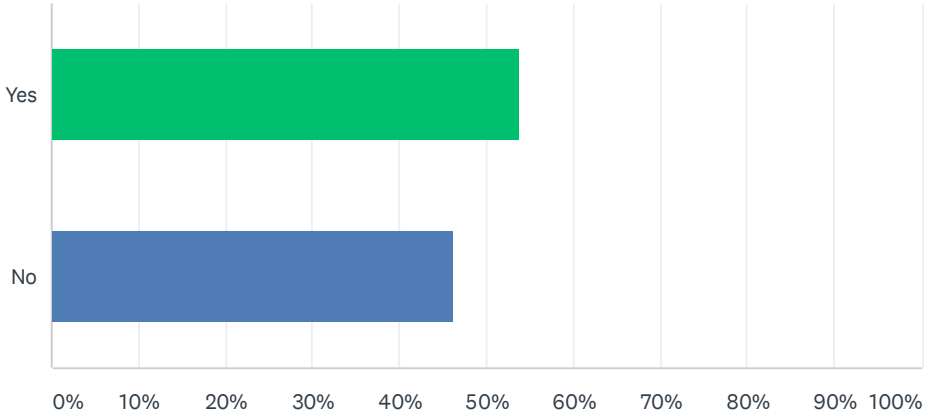
Q10 For which enzymes do you typically have high confidence in the estimated fm based on preclinical studies? None, or Please list.

Answered: 13 Skipped: 2

#	RESPONSES	DATE
1	None	2/27/2020 1:24 PM
2	CYP enzymes; other enzymes (including transporters) there is not high confidence	2/25/2020 3:30 PM
3	CYP3A4	2/3/2020 4:14 PM
4	CYP3A	1/30/2020 1:03 PM
5	CYP3A4	11/5/2019 7:38 PM
6	CYPs	10/25/2019 2:27 PM
7	Cytochrome P450s	10/14/2019 10:22 PM
8	There is generally high confidence in the overall metabolic CL fm estimations for CYP and UGTs. The level of confidence varies based on specific enzymes identified since chemical inhibitors are not well characterized for all enzymes. • High confidence CYPs (1A2, 2C8, 2C9, 2C19, 2D6, 3A4, 3A5, 2B6) • Low confidence CYPs (1A1, 1B1, 2A6, 2C18, 2E1, 2J2, 3A7, 4A11) • High confidence UGTs (1A1, 1A3, 1A4, 1A6, 1A9, 2B7, 2B15) • Low confidence UGTs (1A5, 1A7, 1A8, 1A10, 2B4, 2B17) The confidence in overall identification of other contributing metabolic routes is generally high (eg SULT, CES, FMO, AOX, etc). However, assignment of metabolic CL fm estimations are lower confidence since IVIVE for these metabolic routes (and the appropriate CL scaling factors) are not as well advanced.	10/11/2019 10:19 PM
9	None	10/11/2019 9:07 PM
10	None	10/11/2019 11:25 AM
11	All CYPs	10/10/2019 2:23 PM
12	CYP3A, CYP2C, CYP1A family of enzymes	10/9/2019 2:38 PM
13	NA	10/3/2019 6:58 PM

Q11 If a compound is stable from stability assays using human liver microsomes or hepatocytes, but studies using recombinant enzymes suggest the compound is metabolized by a polymorphic enzyme, do you determine fm by the polymorphic enzyme?

Answered: 13 Skipped: 2



ANSWER CHOICES	RESPONSES	
Yes	53.85%	7
No	46.15%	6
Total Respondents: 13		

Q12 If you answered "Yes" to Question 11 what are the in vitro tools?

Answered: 7 Skipped: 8

#	RESPONSES	DATE
1	Purified/ recombinate enzyme systems	2/25/2020 3:30 PM
2	Recombinant enzyme, RAF method	1/30/2020 1:03 PM
3	microsomes, rCYPs	10/25/2019 2:27 PM
4	Use relative activity factors (RAF) approach when assessing parent compound disappearance using recombinant human cytochrome P450s.	10/14/2019 10:22 PM
5	No compounds are considered truly metabolically stable unless elimination is confirmed as other (eg exclusively renal). Sensitive LC/MS/MS techniques generally allow identification of metabolites with slow formation rates. Phenotyping of low turnover compounds may be challenging, but utilization of metabolite formation in human hepatocyte relay assays in the presence of chemical inhibitors could inform the metabolic CL fm estimations. Metabolite formation rates in the genotyped tissue fractions could also be employed.	10/11/2019 10:19 PM
6	Hepatopac used to confirm metabolism	10/10/2019 2:23 PM
7	recombinant enzymes if available.	10/9/2019 2:38 PM

Q13 What methods do you typically employ in preclinical studies to predict the ft (fraction transported) by particular transporters? Please describe.

Answered: 11 Skipped: 4

#	RESPONSES	DATE
1	None	2/27/2020 1:24 PM
2	Selective chemical inhibitors (based on literature) or knockout rodent models, if available	2/25/2020 3:30 PM
3	none	11/5/2019 7:38 PM
4	CACO2 cells	10/25/2019 2:27 PM
5	None	10/14/2019 10:22 PM
6	Single transfects and primary human hepatocytes with selective inhibitors	10/11/2019 10:19 PM
7	a polarized monolayer of MDCK-II cells grown on permeable supports	10/11/2019 9:07 PM
8	NA	10/11/2019 11:25 AM
9	Not routinely used.	10/10/2019 2:23 PM
10	Crypreserved human hepatocytes and overexpressing cells are used. Using OATP1B1 reference substrates the RAF method is used to predict in vivo CLint,all of test OATP1B1 substrate drugs from OATP1B1-transfected cells.	10/9/2019 2:38 PM
11	NA	10/3/2019 6:58 PM

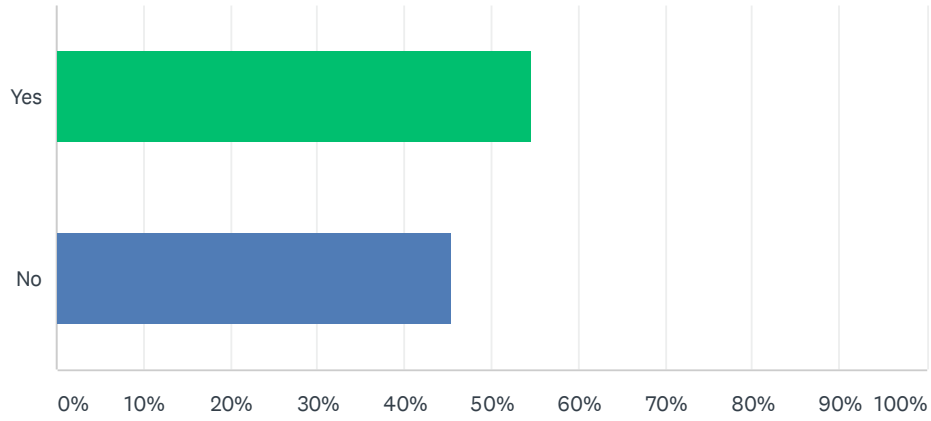
Q14 For which transporters do you typically have high confidence in the estimated ft based on preclinical studies? None, or Please List

Answered: 11 Skipped: 4

#	RESPONSES	DATE
1	None	2/27/2020 1:24 PM
2	No, low confidence	2/25/2020 3:30 PM
3	no	11/5/2019 7:38 PM
4	none	10/25/2019 2:27 PM
5	none	10/14/2019 10:22 PM
6	OCT1 and NTCP. OATPs vs non-OATPs in human hepatocytes.	10/11/2019 10:19 PM
7	none	10/11/2019 9:07 PM
8	NONE	10/11/2019 11:25 AM
9	none	10/10/2019 2:23 PM
10	OATP1B1 and OATP1B3	10/9/2019 2:38 PM
11	NA	10/3/2019 6:58 PM

Q15 Have the preclinical strategies at your company failed to identify enzymes or transporters that were later (e.g. at the time of the human ADME study) determined to be clinically important?

Answered: 11 Skipped: 4



ANSWER CHOICES	RESPONSES	
Yes	54.55%	6
No	45.45%	5
TOTAL		11

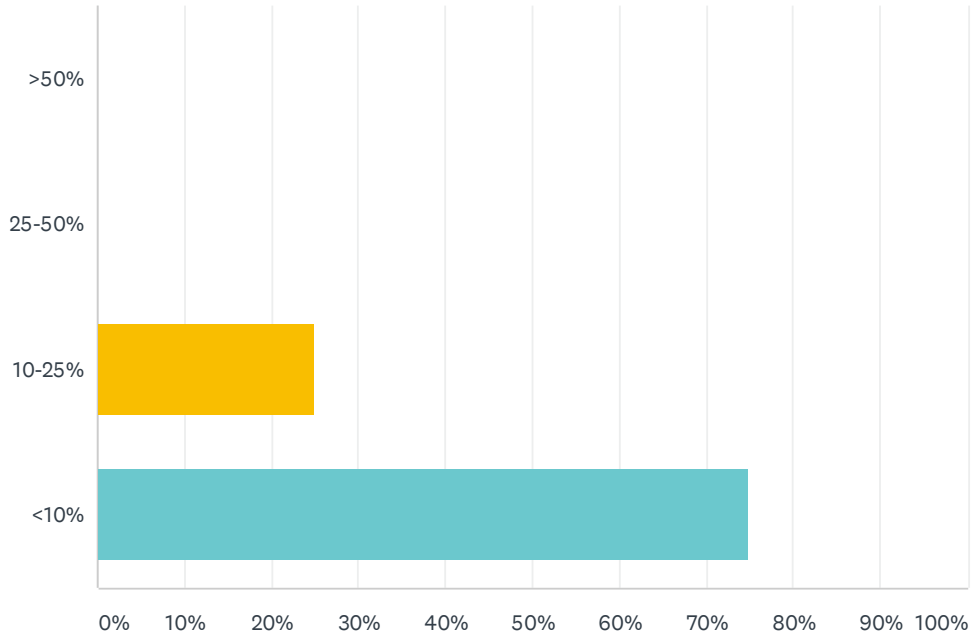
Q16 If you answered "Yes" to Question 15 what was determined to be the reason these enzymes were missed as part of pre-clinical evaluations?

Answered: 7 Skipped: 8

#	RESPONSES	DATE
1	Unable to determine.	2/27/2020 1:24 PM
2	Lack of testing, tools were not available at the time	2/25/2020 3:30 PM
3	na	10/25/2019 2:27 PM
4	. Low clearance compounds in vitro studies	10/14/2019 10:22 PM
5	Inability of evaluated tissue fractions to generate all the human metabolites (eg incomplete metabolic picture or extrahepatic metabolite formation). • Insufficient evaluation of non-CYP enzymes in phenotyping. • Underprediction of in vivo human CL for certain metabolic routes due to lack in IVIVE (eg AOX, esterases, etc). • Previous use of screening r-CYP phenotyping – since strategy corrected with learnings.	10/11/2019 10:19 PM
6	UGT2B17 – wasn’t routinely analyzed at the time	10/10/2019 2:23 PM
7	Lack of appropriate in vitro tools, Lack of knowledge about the extrahepatic or hepatic expression of enzymes.	10/9/2019 2:38 PM

Q17 What percent of small-molecule compounds in your pipeline are metabolized or transported at least in part by CYP2D6?

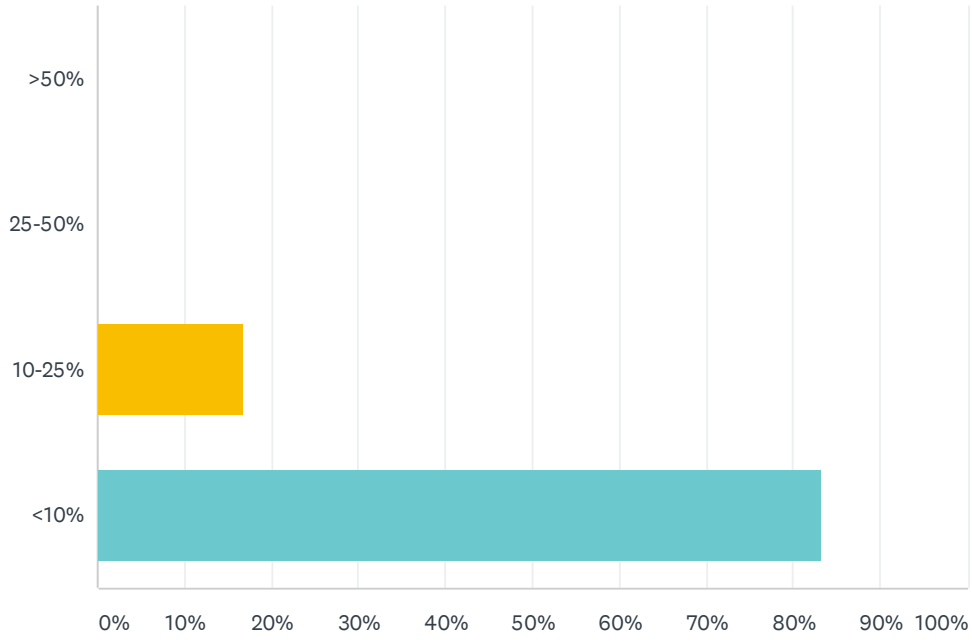
Answered: 12 Skipped: 3



ANSWER CHOICES	RESPONSES	
>50%	0.00%	0
25-50%	0.00%	0
10-25%	25.00%	3
<10%	75.00%	9
TOTAL		12

Q18 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C19?

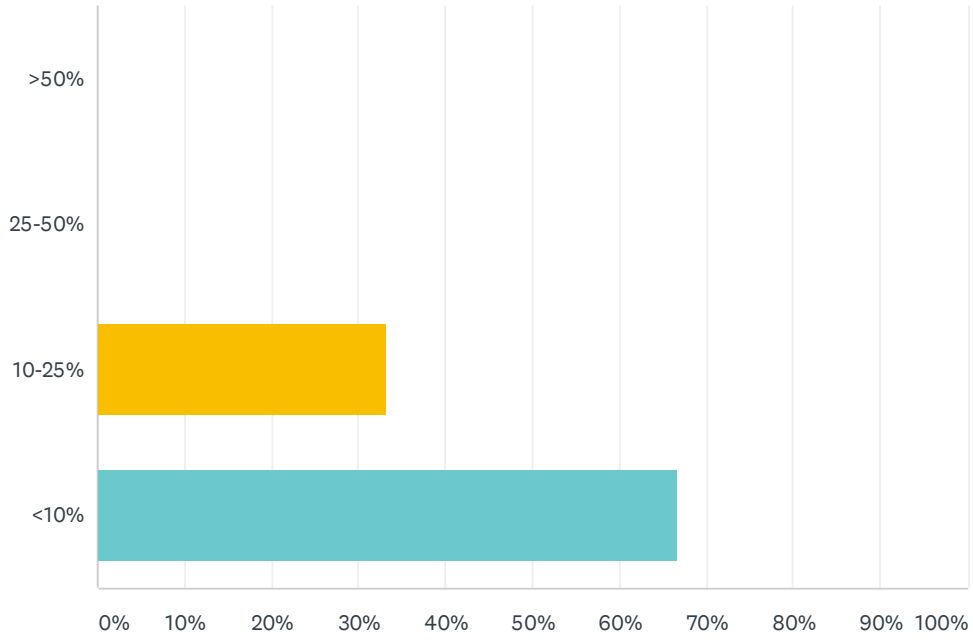
Answered: 12 Skipped: 3



ANSWER CHOICES	RESPONSES	
>50%	0.00%	0
25-50%	0.00%	0
10-25%	16.67%	2
<10%	83.33%	10
TOTAL		12

Q19 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C9?

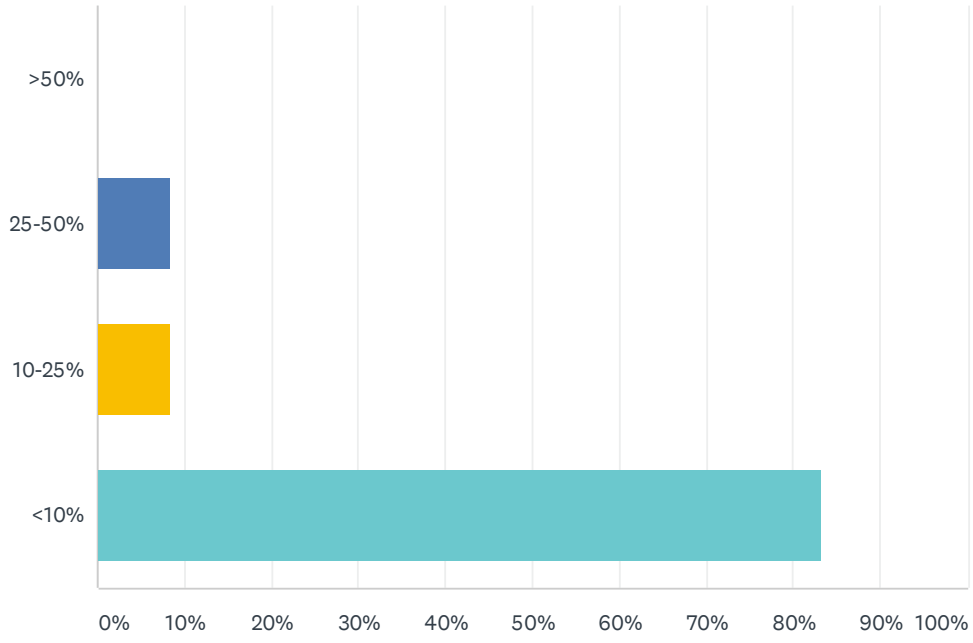
Answered: 12 Skipped: 3



ANSWER CHOICES	RESPONSES	
>50%	0.00%	0
25-50%	0.00%	0
10-25%	33.33%	4
<10%	66.67%	8
TOTAL		12

Q20 What percent of small-molecule compounds in your pipeline are metabolized at least in part by UGT1A1?

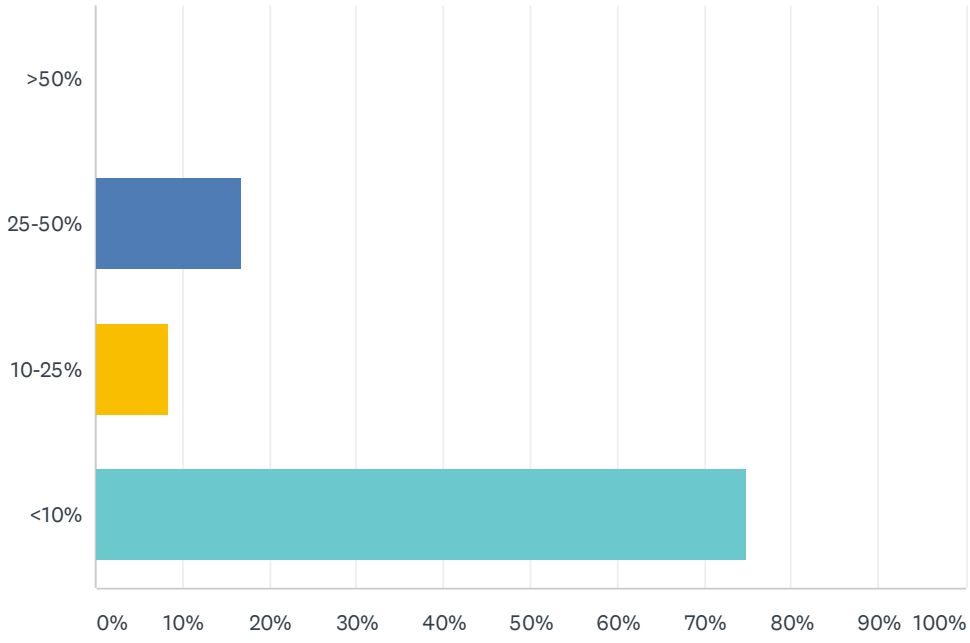
Answered: 12 Skipped: 3



ANSWER CHOICES	RESPONSES	
>50%	0.00%	0
25-50%	8.33%	1
10-25%	8.33%	1
<10%	83.33%	10
TOTAL		12

Q21 What percent of small-molecule compounds in your pipeline are transported at least in part by SLCO1B1?

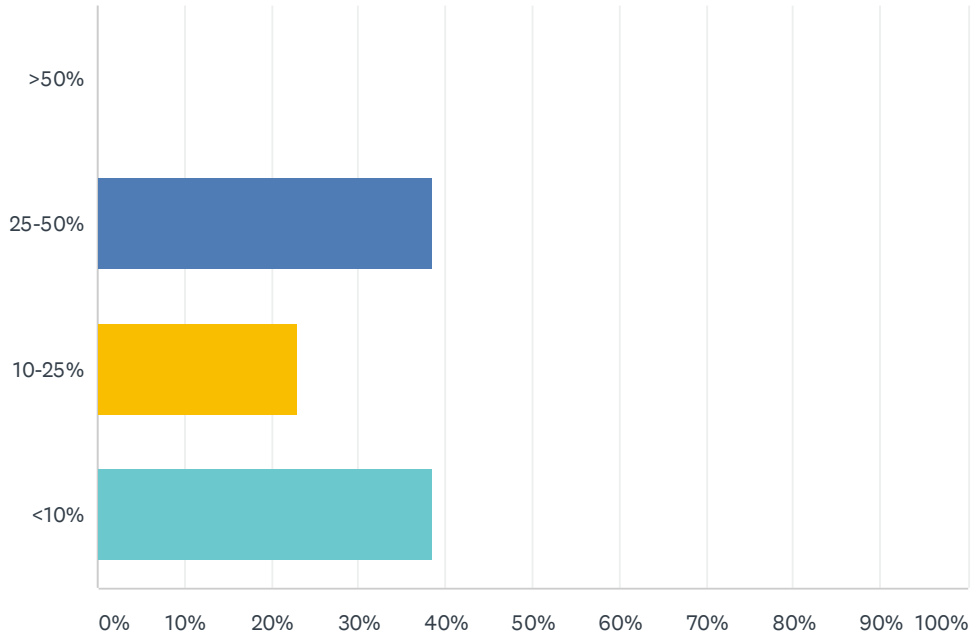
Answered: 12 Skipped: 3



ANSWER CHOICES	RESPONSES	
>50%	0.00%	0
25-50%	16.67%	2
10-25%	8.33%	1
<10%	75.00%	9
TOTAL		12

Q22 What percent of small-molecule compounds in your pipeline are transported at least in part by BCRP?

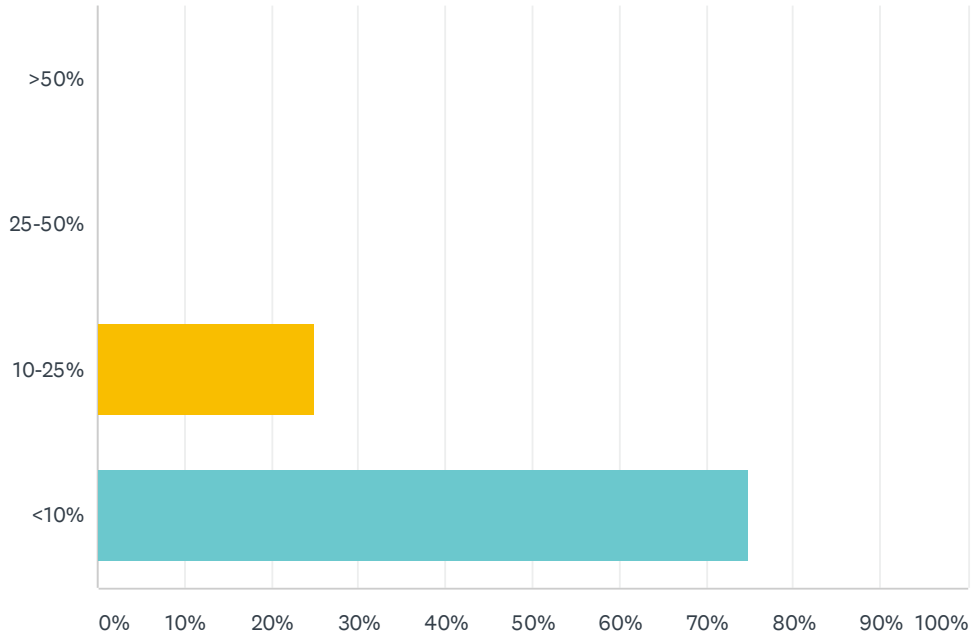
Answered: 13 Skipped: 2



ANSWER CHOICES	RESPONSES	
>50%	0.00%	0
25-50%	38.46%	5
10-25%	23.08%	3
<10%	38.46%	5
TOTAL		13

Q23 What percent of small-molecule compounds in your pipeline are transported at least in part by OCT1?

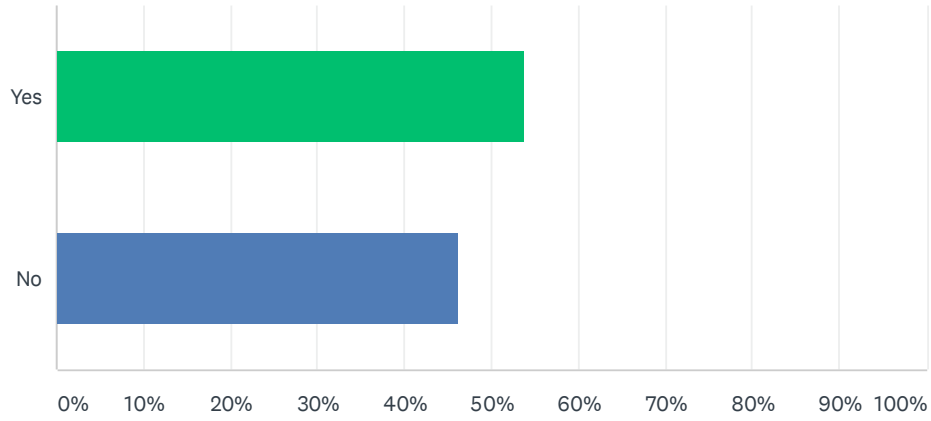
Answered: 12 Skipped: 3



ANSWER CHOICES	RESPONSES	
>50%	0.00%	0
25-50%	0.00%	0
10-25%	25.00%	3
<10%	75.00%	9
TOTAL		12

Q24 Do you use modeling and simulation tools to predict the impact of genetic variants in enzymes/transporters on compound disposition prior to clinical studies?

Answered: 13 Skipped: 2



ANSWER CHOICES	RESPONSES	
Yes	53.85%	7
No	46.15%	6
TOTAL		13

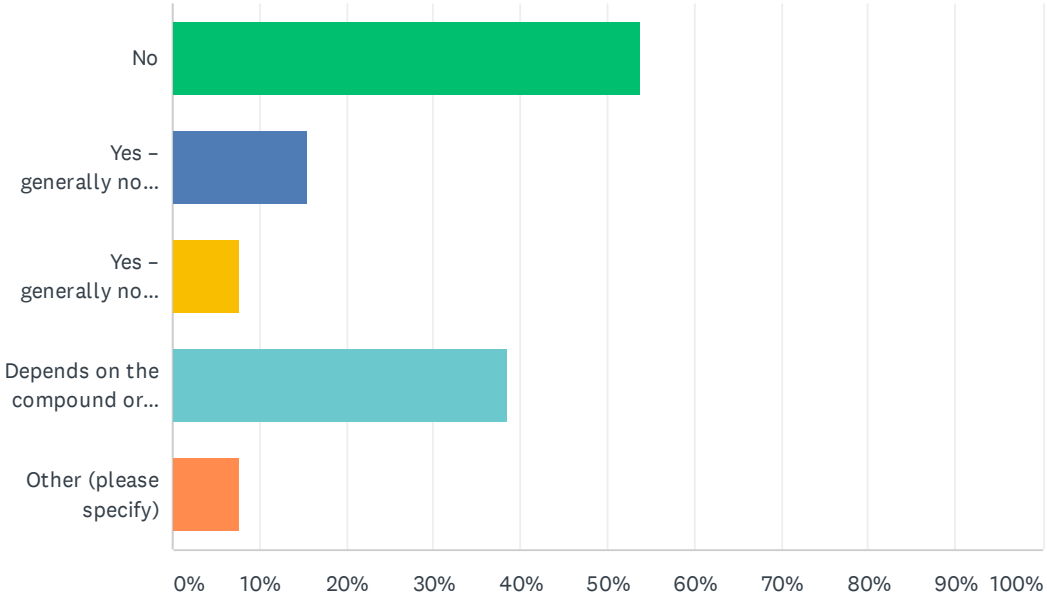
Q25 If you answered "Yes" to Question 24, please describe scenarios in which such tools may be used and what software is being used:

Answered: 8 Skipped: 7

#	RESPONSES	DATE
1	Highly situation-dependent.	2/27/2020 1:24 PM
2	SIMCYP	2/25/2020 3:30 PM
3	Commonly used- SimCYP to look at variants in CYP2C	2/3/2020 4:14 PM
4	pediatrics, simcyp	11/5/2019 7:38 PM
5	na	10/25/2019 2:27 PM
6	In cases where polymorphic enzymes contribute to <25% of the metabolic CL fm or CL fm, limited if any evaluations are generally considered. In cases where metabolic CL fm or CL fm exceeds 25% and particularly 50%, the impact of genotype on overall CL is considered in conjunction with special scenarios (eg CYP2C19 poor metabolizer co-administered a CYP3A inhibitor). We use Simcyp as the preferred PBPK modeling tool. Generally, the questions are if human exposure in poor metabolizer subjects would still be within TI safety margins and/or if co-medications should be excluded in initial clinical trials until in vivo involvement of polymorphic CL is more fully elucidated.	10/11/2019 10:19 PM
7	SimCYP – simulate poor, normal and extensive metabolizers	10/10/2019 2:23 PM
8	We use Simcyp population simulator to explore the DDI in case of a polymorphic enzyme. This is only feasible if the frequency of the polymorphic population is available in the simulator. We also use sensitivity analysis to understand the impact of the polymorphic enzyme on drug exposure and DDI.	10/9/2019 2:38 PM

Q26 Does your company have decision criteria regarding drug candidate progression based on predicted involvement (%) of an enzyme or transporter with genetic variants that might impact clearance? Select all that apply.

Answered: 13 Skipped: 2

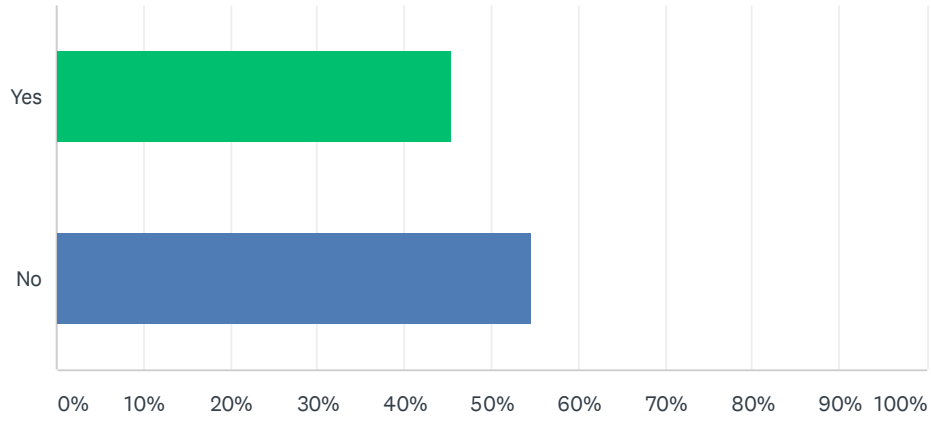


ANSWER CHOICES	RESPONSES	
No	53.85%	7
Yes – generally no progression with over 50% contribution of enzyme	15.38%	2
Yes – generally no progression with over 50% contribution of transporter	7.69%	1
Depends on the compound or therapeutic area (please describe further – fill in)	38.46%	5
Other (please specify)	7.69%	1
Total Respondents: 13		

#	OTHER (PLEASE SPECIFY)	DATE
1	In general, the aim is to identify molecules where less than 50% of the CL involves a polymorphic enzyme or transporter. In certain cases, it is easier to minimize routes (eg no enzyme for CYP2D6), whereas reduced function enzymes may be less critically evaluated (eg CYP2C9, CYP2C19) and requires further experimentation. In other cases, impact of polymorphic transporters would be implied (eg OATP1B1 when targeting the liver) and is evaluated with impact on PK variability and patient safety. This strategy also includes assessment in genotyped/phenotyped microsomes.	10/11/2019 10:19 PM

Q27 If your company advances drug candidates with a predicted significant involvement of a polymorphic enzyme or transporter in clearance, are further pre-clinical studies performed to assess the risks?

Answered: 11 Skipped: 4



ANSWER CHOICES	RESPONSES	
Yes	45.45%	5
No	54.55%	6
TOTAL		11

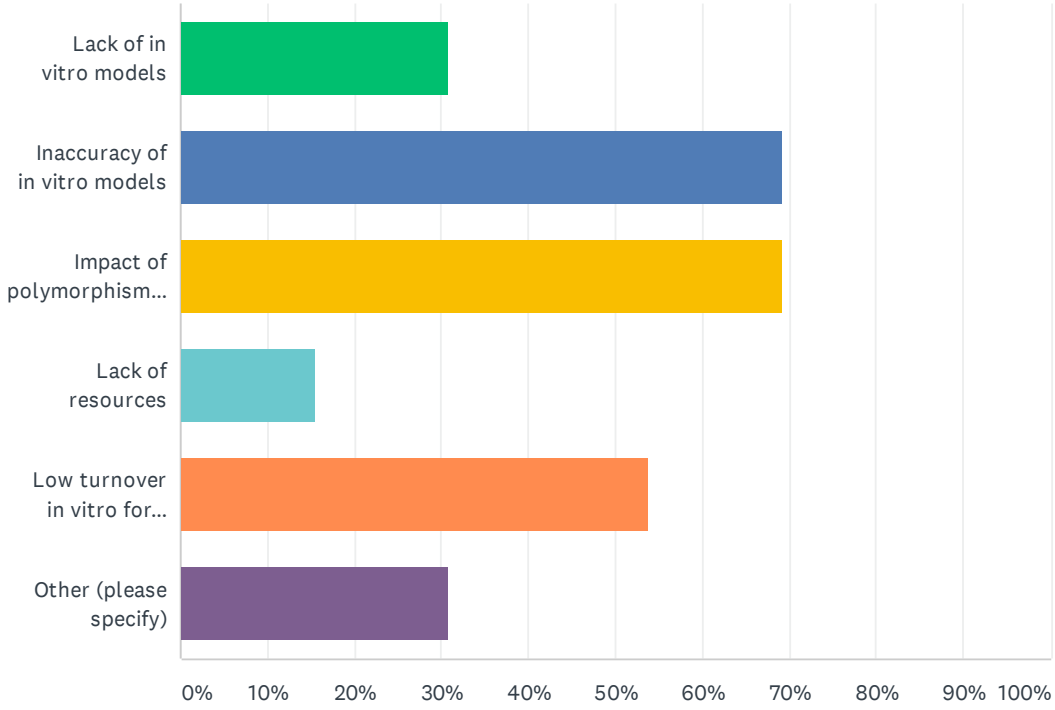
Q28 If you answered "Yes" to Question 27 please describe (e.g. use of genotyped hepatocytes, recombinant systems expressing variant. Please include specific enzymes/transporters and alleles assayed using a given method.)

Answered: 5 Skipped: 10

#	RESPONSES	DATE
1	Highly situation-dependent.	2/27/2020 1:24 PM
2	major isozymes	10/25/2019 2:27 PM
3	In general, we would evaluate genotyped human liver microsomes (more donors are readily available) and sometimes genotyped hepatocytes (less donors available). We have not used variant expressed enzymes. Primary evaluations include CYPs (eg 2C9, 2C19, 2D6, 3A5), SLCO1B1, and UGTs (eg 1A1) where clinically significant polymorphisms are known.	10/11/2019 10:19 PM
4	.) In select cases have determined intrinsic clearance in hepatocytes from pre-genotyped donors with CYP2C19*1/*1 (wild type) and CYP2C19*2/*2 as well as CYP2C19*3/*3 (poor metabolizer). Use of polymorphic enzymes is being considered, but not currently in use.	10/10/2019 2:23 PM
5	We used recombinant systems that express the variant. Additionally we use PBPK modeling to understand the impact of these polymorphisms. These simulations are then used to make decisions on clinical study design, clinical pharmacology planning.	10/9/2019 2:38 PM

Q29 What gaps do you see in the ability to determine the impact of enzymes with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.

Answered: 13 Skipped: 2

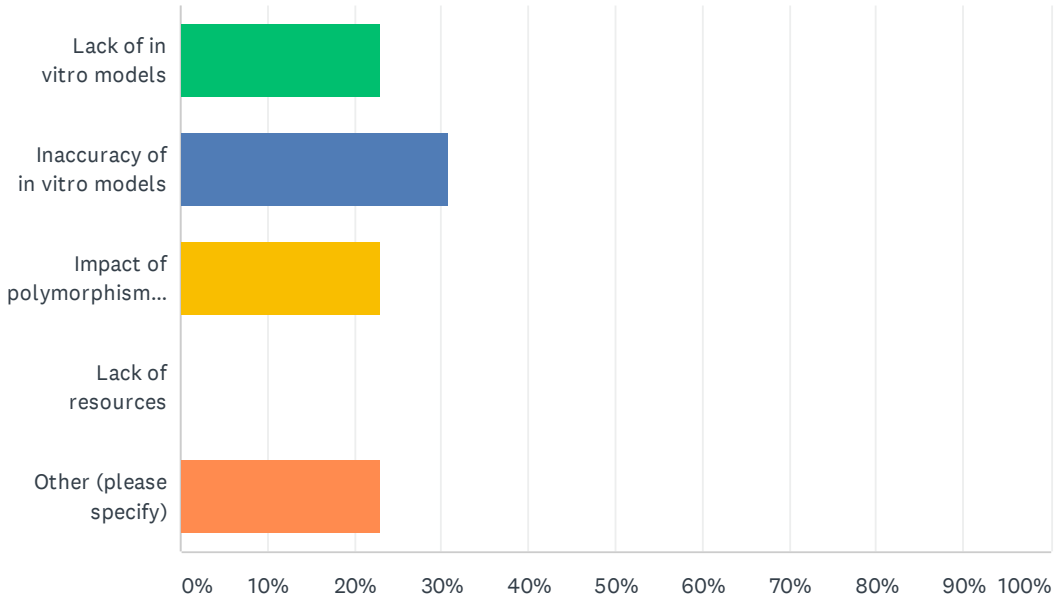


ANSWER CHOICES	RESPONSES	
Lack of in vitro models	30.77%	4
Inaccuracy of in vitro models	69.23%	9
Impact of polymorphisms is not well characterized	69.23%	9
Lack of resources	15.38%	2
Low turnover in vitro for certain compounds	53.85%	7
Other (please specify)	30.77%	4
Total Respondents: 13		

#	OTHER (PLEASE SPECIFY)	DATE
1	Complexity of systems - unknown variables and variable attributes.	2/27/2020 1:24 PM
2	Scaling factors are not well characterized.	10/14/2019 10:22 PM
3	PBPK models are not fully developed and verified to model clinical significance (PK) of certain polymorphisms (eg CYP2C19). In other cases (eg OATP, CYP3A5), PK variability may increase but may not impact clinical outcome or efficacy (PD) and altered PK variability may not require therapeutic dose adjustments. More clinical data relating genotype with PK variability and outcome are required, eg it is well understood that PK could be impacted by polymorphic CYP2C19 expression, but the exact impact of each polymorphism on PK (eg percentage reduction in PM metabolic rate) is less clearly understood. In addition, difficulties of low turnover and understanding the full impact of polymorphisms (genotype-phenotype translation).	10/11/2019 10:19 PM
4	combination of enzymes+transporters	10/10/2019 2:23 PM

Q30 What gaps do you see in the ability to determine the impact of transporters with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.

Answered: 13 Skipped: 2



ANSWER CHOICES	RESPONSES	
Lack of in vitro models	23.08%	3
Inaccuracy of in vitro models	30.77%	4
Impact of polymorphisms is not well characterized	23.08%	3
Lack of resources	0.00%	0
Other (please specify)	23.08%	3
TOTAL		13

#	OTHER (PLEASE SPECIFY)	DATE
1	Scaling factors are not well characterized.	10/14/2019 10:22 PM
2	The clinical impact of transporter pharmacogenomics on patient safety and therapeutic drug efficacy is less clear (eg OATP variants impact PK variability and safety of simvastatin and has no impact of efficacy of atorvastatin). Clinical studies with genotype as covariate relating PK variability (potential safety marker) as well as clinical efficacy (outcome) are required to advance the field. Instead of all bottom-up, more top-down data are required to eventually meet with a middle-out approach and help to context the value of in vitro tool evaluations in the preclinical phases of drug discovery and development.	10/11/2019 10:19 PM
3	Inaccuracy of in vitro models; Impact of polymorphisms is not well characterized; Other: contradictory clinical data for some transporters such as OCT1 and MDR1 P-gp)	10/10/2019 2:23 PM