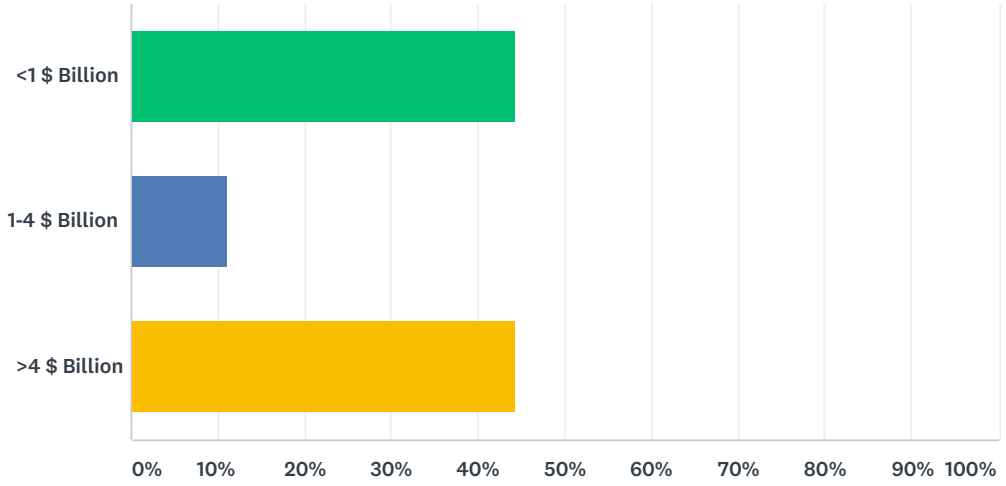
Q1 Please enter your unique individual Survey Monkey Code that was sent to you by Julian Arbuckle:

Answered: 8 Skipped: 1

#	RESPONSES	DATE
1	5965	10/25/2019 1:27 PM
2	2088	10/14/2019 9:22 PM
3	4001	10/11/2019 9:19 PM
4	4099	10/11/2019 8:07 PM
5	7755	10/11/2019 10:25 AM
6	3078	10/10/2019 1:23 PM
7	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 1:38 PM
8	5351	10/1/2019 5:35 PM

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

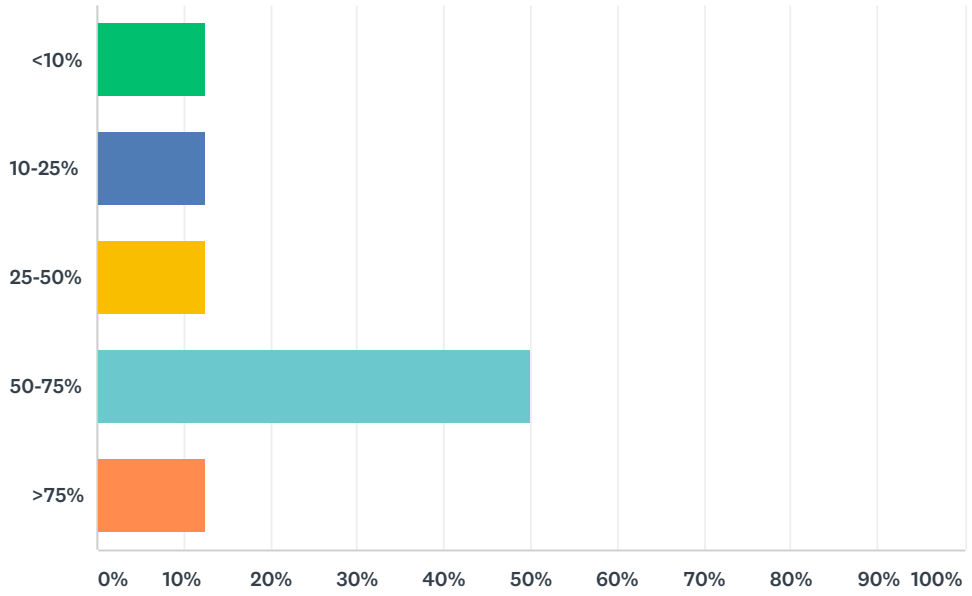
Answered: 9 Skipped: 0



ANSWER CHOICES	RESPONSES	
<1 $ Billion	44.44%	4
1-4 $ Billion	11.11%	1
>4 $ Billion	44.44%	4
TOTAL		9

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

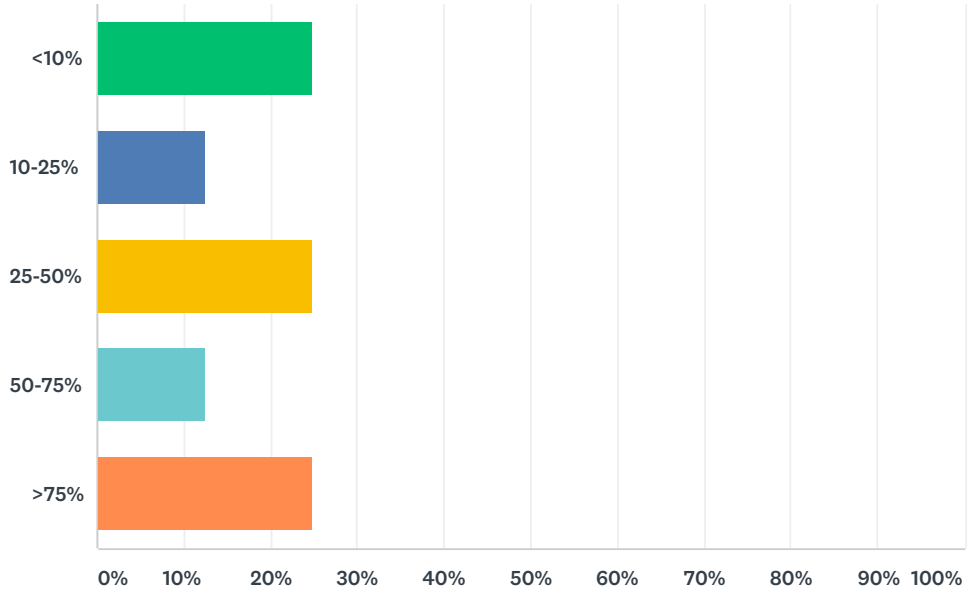
Answered: 8 Skipped: 1



ANSWER CHOICES	RESPONSES	
<10%	12.50%	1
10-25%	12.50%	1
25-50%	12.50%	1
50-75%	50.00%	4
>75%	12.50%	1
TOTAL		8

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

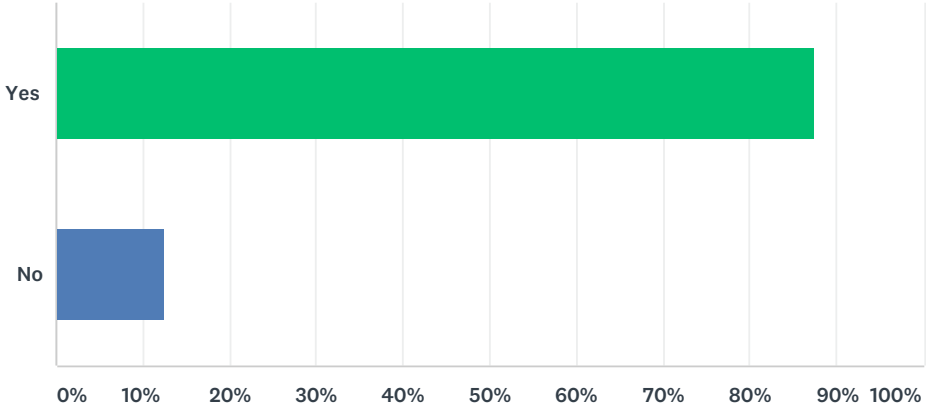
Answered: 8 Skipped: 1



ANSWER CHOICES	RESPONSES	
<10%	25.00%	2
10-25%	12.50%	1
25-50%	25.00%	2
50-75%	12.50%	1
>75%	25.00%	2
TOTAL		8

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?

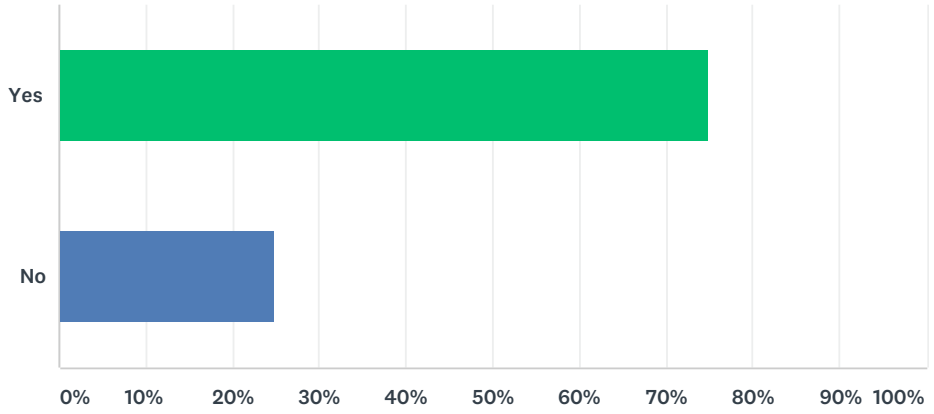
Answered: 8 Skipped: 1



ANSWER CHOICES	RESPONSES	
Yes	87.50%	7
No	12.50%	1
TOTAL		8

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?

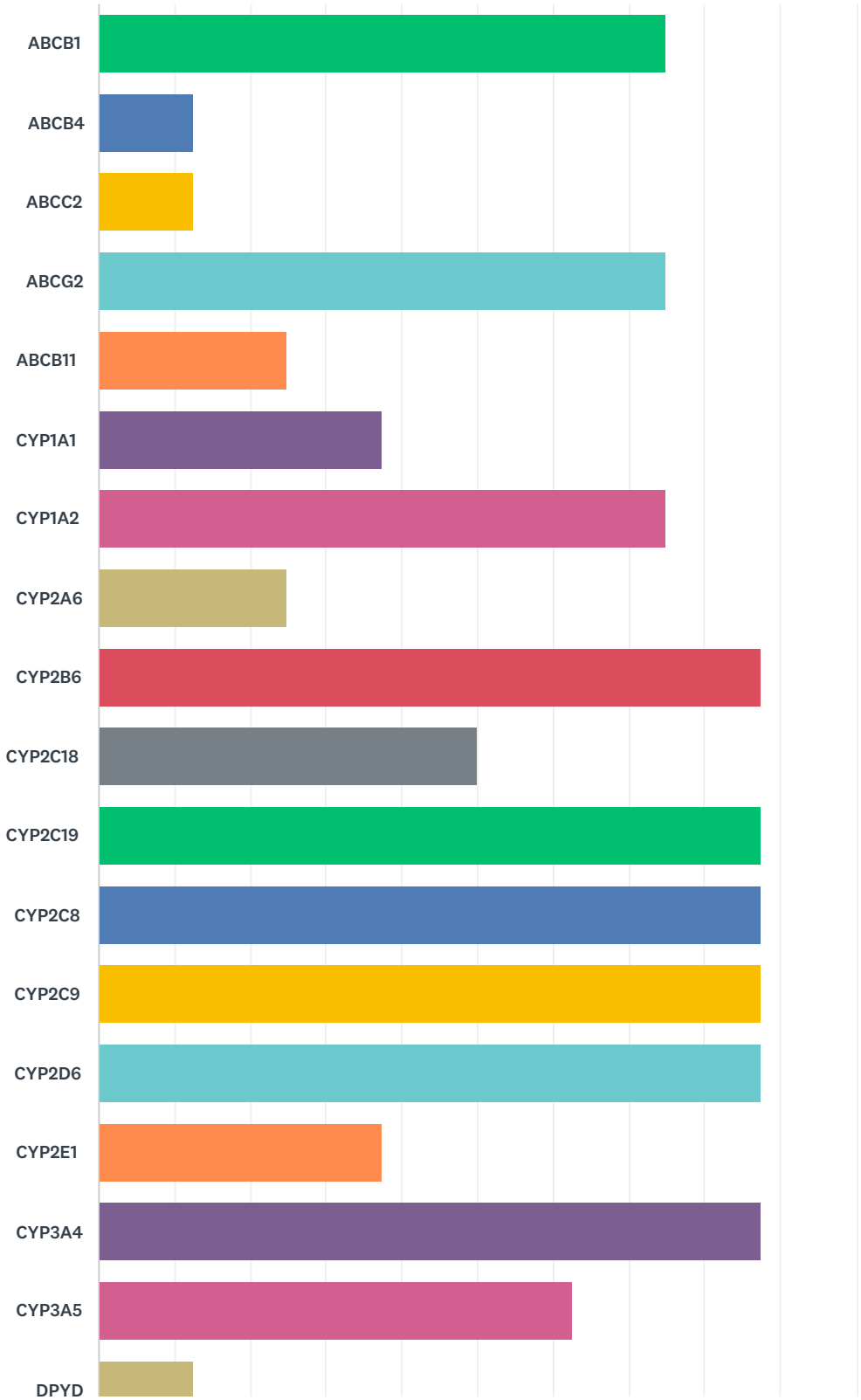
Answered: 8 Skipped: 1

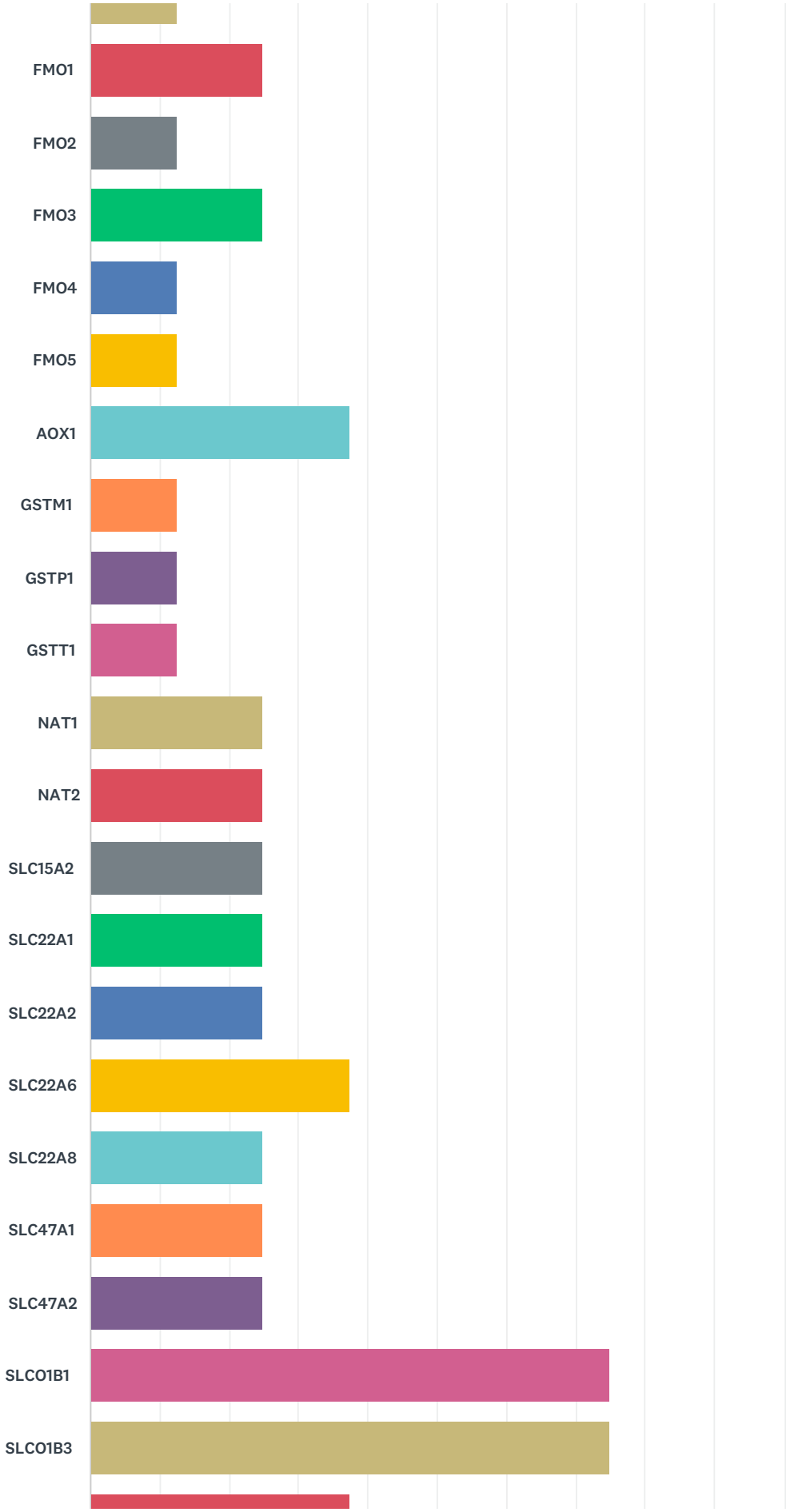


ANSWER CHOICES	RESPONSES	
Yes	75.00%	6
No	25.00%	2
TOTAL		8

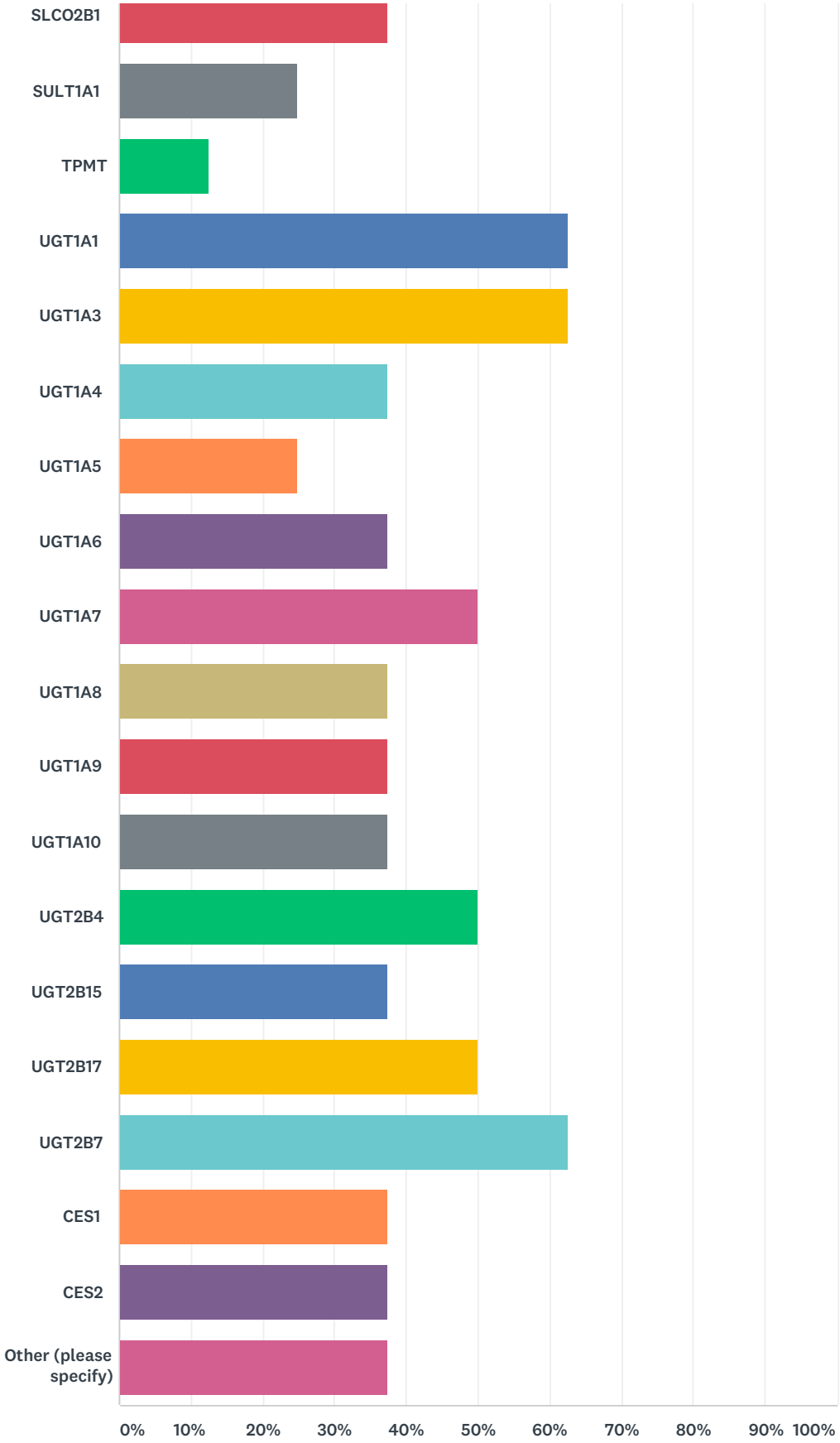
Q7 Which enzymes and transporters does your company test in vitro for their involvement in clearance of discovery or development compounds prior to phase 1 clinical studies? Select all that apply.

Answered: 8 Skipped: 1




FMO1
FMO2
FMO3
FMO4
FMO5
AOX1
GSTM1
GSTP1
GSTT1
NAT1
NAT2
SLC15A2
SLC22A1
SLC22A2
SLC22A6
SLC22A8
SLC47A1
SLC47A2
SLCO1B1
SLCO1B3

Current ADME PGx Preclinical Strategy/Implmentation



ANSWER CHOICES	RESPONSES

ABCB1	75.00%	6
ABCB4	12.50%	1
ABCC2	12.50%	1
ABCG2	75.00%	6
ABCB11	25.00%	2
CYP1A1	37.50%	3
CYP1A2	75.00%	6
CYP2A6	25.00%	2
CYP2B6	87.50%	7
CYP2C18	50.00%	4
CYP2C19	87.50%	7
CYP2C8	87.50%	7
CYP2C9	87.50%	7
CYP2D6	87.50%	7
CYP2E1	37.50%	3
CYP3A4	87.50%	7
CYP3A5	62.50%	5
DPYD	12.50%	1
FMO1	25.00%	2
FMO2	12.50%	1
FMO3	25.00%	2
FMO4	12.50%	1
FMO5	12.50%	1
AOX1	37.50%	3
GSTM1	12.50%	1
GSTP1	12.50%	1
GSTT1	12.50%	1
NAT1	25.00%	2
NAT2	25.00%	2
SLC15A2	25.00%	2
SLC22A1	25.00%	2
SLC22A2	25.00%	2
SLC22A6	37.50%	3
SLC22A8	25.00%	2

SLC47A1	25.00%	2
SLC47A2	25.00%	2
SLCO1B1	75.00%	6
SLCO1B3	75.00%	6
SLCO2B1	37.50%	3
SULT1A1	25.00%	2
TPMT	12.50%	1
UGT1A1	62.50%	5
UGT1A3	62.50%	5
UGT1A4	37.50%	3
UGT1A5	25.00%	2
UGT1A6	37.50%	3
UGT1A7	50.00%	4
UGT1A8	37.50%	3
UGT1A9	37.50%	3
UGT1A10	37.50%	3
UGT2B4	50.00%	4
UGT2B15	37.50%	3
UGT2B17	50.00%	4
UGT2B7	62.50%	5
CES1	37.50%	3
CES2	37.50%	3
Other (please specify)	37.50%	3
Total Respondents: 8		

#	OTHER (PLEASE SPECIFY)	DATE
1	CYP2J2	10/14/2019 9:22 PM
2	UGT2B10, MAOA, MAOB	10/11/2019 10:25 AM
3	nucleases, which is well understood already for the platform	10/3/2019 5:58 PM

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

Answered: 5 Skipped: 4

#	RESPONSES	DATE
1	no	10/25/2019 1:27 PM
2	• 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 9:19 PM
3	none	10/10/2019 1:23 PM
4	MDR1 and MRP2	10/9/2019 1:38 PM
5	No	10/3/2019 5:58 PM

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

Answered: 8 Skipped: 1

#	RESPONSES	DATE
1	in vitro metabolism studies	10/25/2019 1:27 PM
2	. parent compound disappearance using recombinant human cytochrome P450s . human hepatocytes with and without ABT	10/14/2019 9:22 PM
3	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 9:19 PM
4	measuring substrate loss in individual cDNA expressed P450s	10/11/2019 8:07 PM
5	Recombinant enzymes and hepatocytes with specific inhibitor followed by in vitro-in vivo scaling	10/11/2019 10:25 AM
6	Recombinant enzymes and ISEF approaches for CYPs, human liver microsomes with specific inhibitors and inhibitory antibodies are used as well	10/10/2019 1:23 PM
7	recombinant enzymes using the RAF method, inhibition with specific inhibitors in human hepatocytes or microsomes.	10/9/2019 1:38 PM
8	no applicable for RNA drugs	10/3/2019 5:58 PM

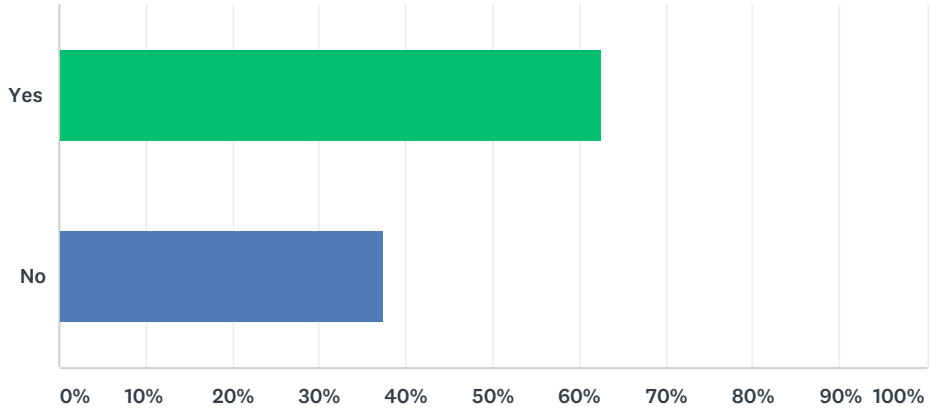
Q10 For which enzymes do you typically have high confidence in the estimated fm based on preclinical studies? None, or Please list.

Answered: 8 Skipped: 1

#	RESPONSES	DATE
1	CYPs	10/25/2019 1:27 PM
2	Cytochrome P450s	10/14/2019 9:22 PM
3	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 9:19 PM
4	None	10/11/2019 8:07 PM
5	None	10/11/2019 10:25 AM
6	All CYPs	10/10/2019 1:23 PM
7	CYP3A, CYP2C, CYP1A family of enzymes	10/9/2019 1:38 PM
8	NA	10/3/2019 5:58 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: 8 Skipped: 1



ANSWER CHOICES	RESPONSES	
Yes	62.50%	5
No	37.50%	3
Total Respondents: 8		

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

Answered: 5 Skipped: 4

#	RESPONSES	DATE
1	microsomes, rCYPs	10/25/2019 1:27 PM
2	Use relative activity factors (RAF) approach when assessing parent compound disappearance using recombinant human cytochrome P450s.	10/14/2019 9:22 PM
3	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 9:19 PM
4	Hepatopac used to confirm metabolism	10/10/2019 1:23 PM
5	recombinant enzymes if available.	10/9/2019 1:38 PM

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

Answered: 8 Skipped: 1

#	RESPONSES	DATE
1	CACO2 cells	10/25/2019 1:27 PM
2	None	10/14/2019 9:22 PM
3	Single transfects and primary human hepatocytes with selective inhibitors	10/11/2019 9:19 PM
4	a polarized monolayer of MDCK-II cells grown on permeable supports	10/11/2019 8:07 PM
5	NA	10/11/2019 10:25 AM
6	Not routinely used.	10/10/2019 1:23 PM
7	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 1:38 PM
8	NA	10/3/2019 5:58 PM

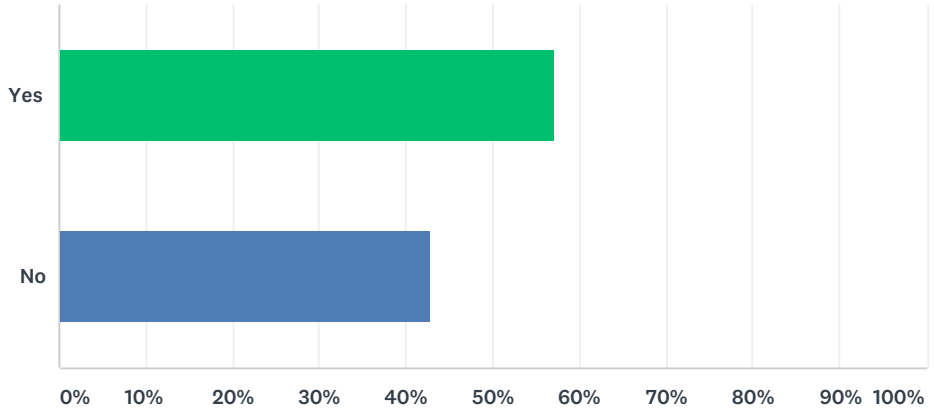
Q14 For which transporters do you typically have high confidence in the estimated ft based on preclinical studies? None, or Please List

Answered: 8 Skipped: 1

#	RESPONSES	DATE
1	none	10/25/2019 1:27 PM
2	none	10/14/2019 9:22 PM
3	OCT1 and NTCP. OATPs vs non-OATPs in human hepatocytes.	10/11/2019 9:19 PM
4	none	10/11/2019 8:07 PM
5	NONE	10/11/2019 10:25 AM
6	none	10/10/2019 1:23 PM
7	OATP1B1 and OATP1B3	10/9/2019 1:38 PM
8	NA	10/3/2019 5:58 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: 7 Skipped: 2



ANSWER CHOICES	RESPONSES	
Yes	57.14%	4
No	42.86%	3
TOTAL		7

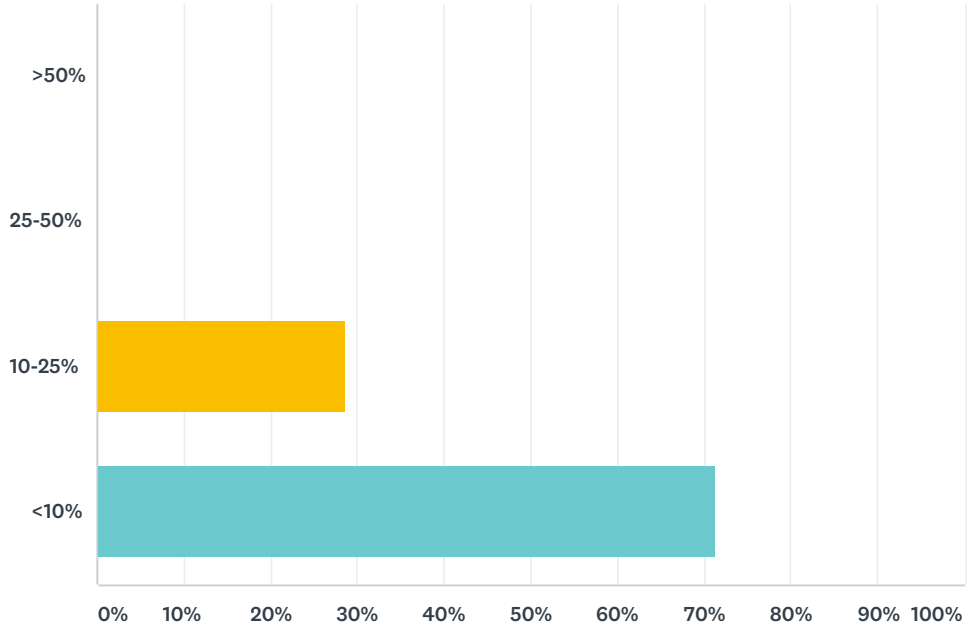
Q16 If you answered "Yes" to Question 15 what was determined to be the reason these enzymes were missed as part of pre-clinical evaluations?

Answered: 5 Skipped: 4

#	RESPONSES	DATE
1	na	10/25/2019 1:27 PM
2	. Low clearance compounds in vitro studies	10/14/2019 9:22 PM
3	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 9:19 PM
4	UGT2B17 – wasn't routinely analyzed at the time	10/10/2019 1:23 PM
5	Lack of appropriate in vitro tools, Lack of knowledge about the extrahepatic or hepatic expression of enzymes.	10/9/2019 1:38 PM

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

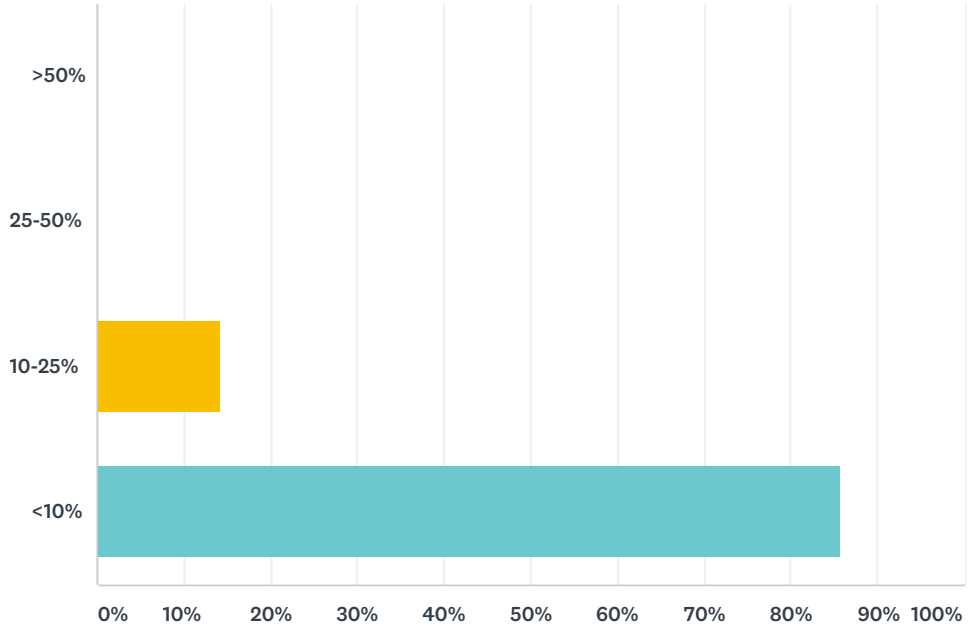
Answered: 7 Skipped: 2



ANSWER CHOICES	RESPONSES	
>50%	0.00%	0
25-50%	0.00%	0
10-25%	28.57%	2
<10%	71.43%	5
TOTAL		7

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

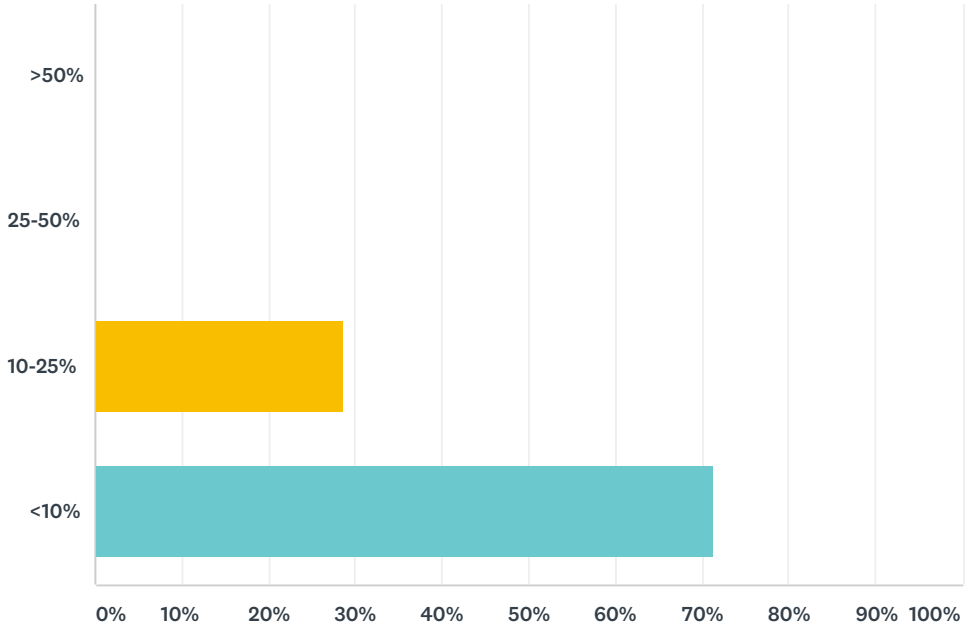
Answered: 7 Skipped: 2



ANSWER CHOICES	RESPONSES	
>50%	0.00%	0
25-50%	0.00%	0
10-25%	14.29%	1
<10%	85.71%	6
TOTAL		7

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

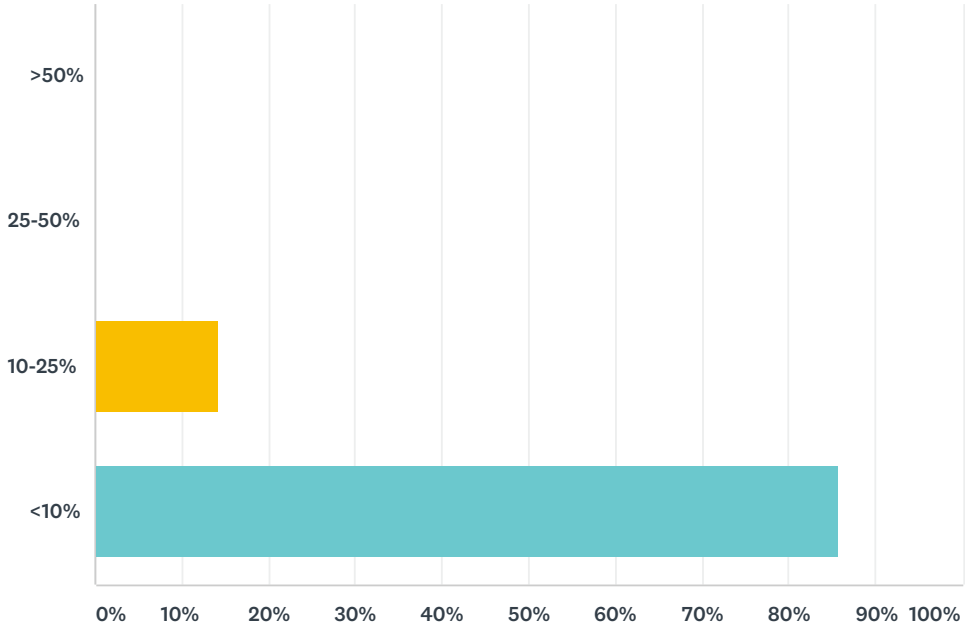
Answered: 7 Skipped: 2



ANSWER CHOICES	RESPONSES	
>50%	0.00%	0
25-50%	0.00%	0
10-25%	28.57%	2
<10%	71.43%	5
TOTAL		7

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

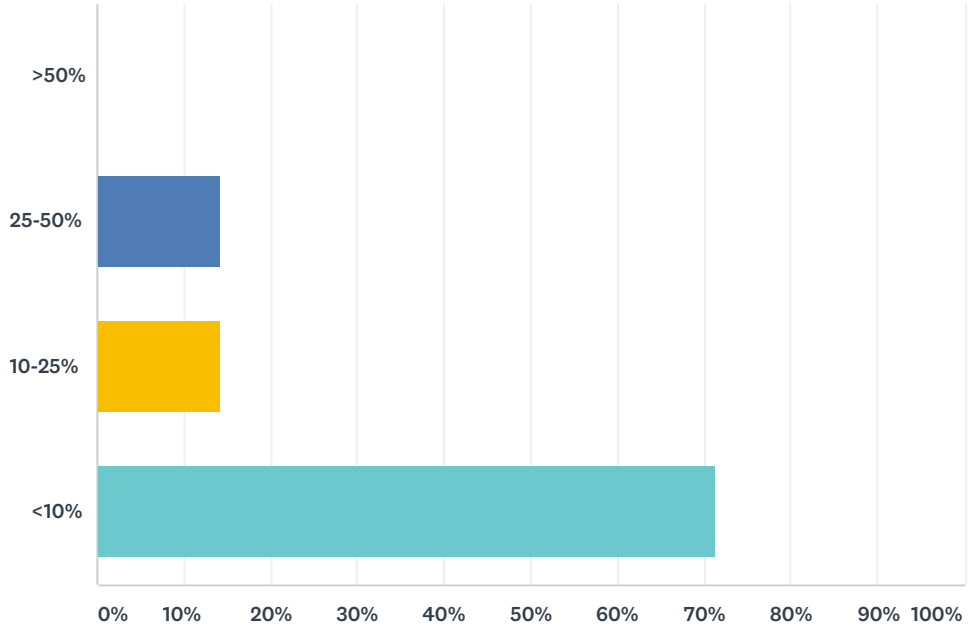
Answered: 7 Skipped: 2



ANSWER CHOICES	RESPONSES	
>50%	0.00%	0
25-50%	0.00%	0
10-25%	14.29%	1
<10%	85.71%	6
TOTAL		7

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

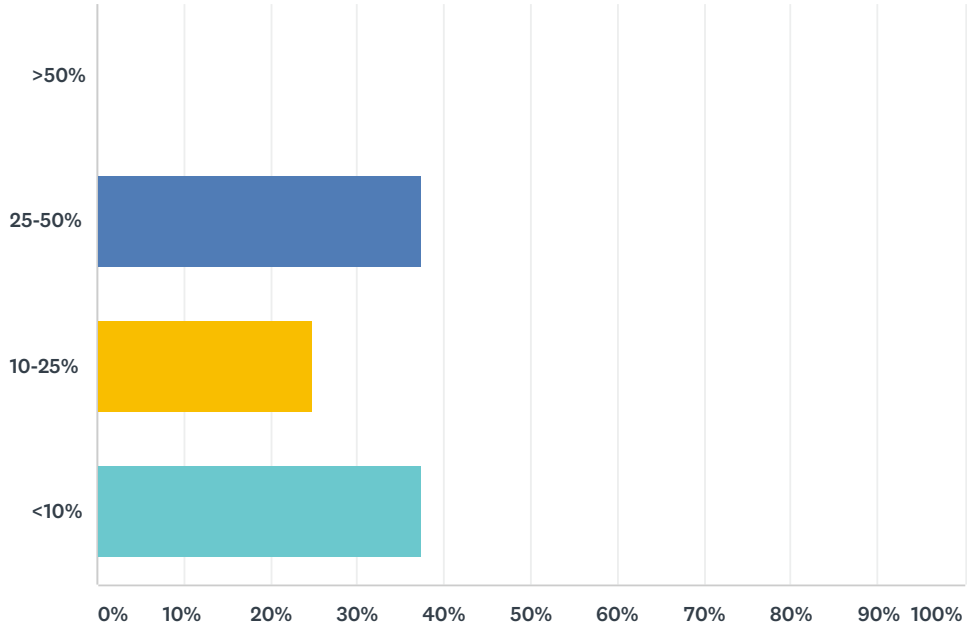
Answered: 7 Skipped: 2



ANSWER CHOICES	RESPONSES	
>50%	0.00%	0
25-50%	14.29%	1
10-25%	14.29%	1
<10%	71.43%	5
TOTAL		7

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

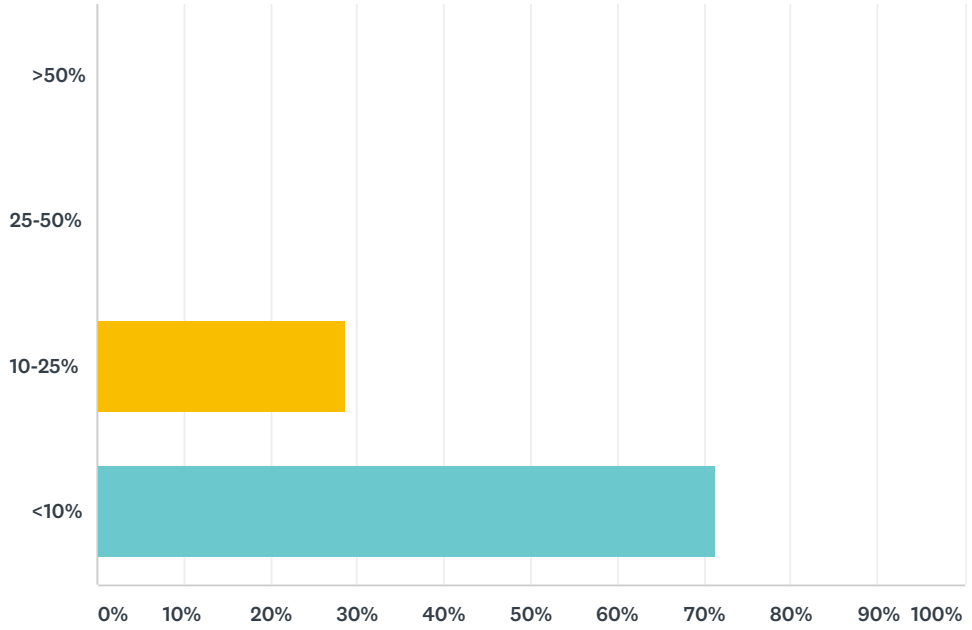
Answered: 8 Skipped: 1



ANSWER CHOICES	RESPONSES	
>50%	0.00%	0
25-50%	37.50%	3
10-25%	25.00%	2
<10%	37.50%	3
TOTAL		8

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

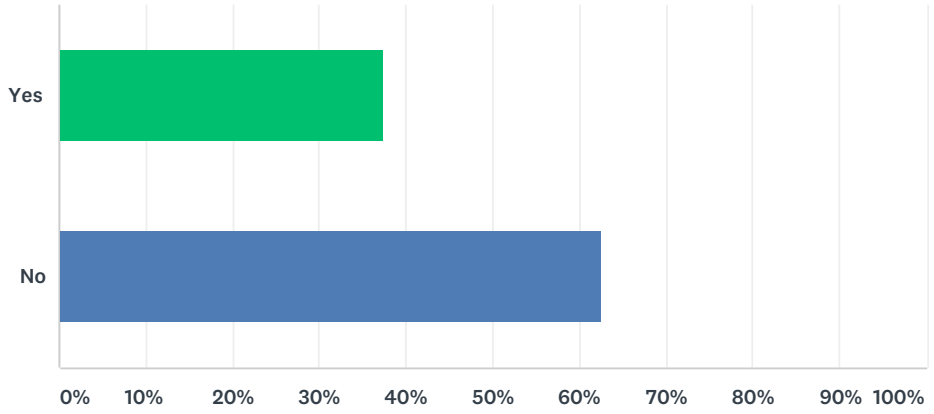
Answered: 7 Skipped: 2



ANSWER CHOICES	RESPONSES	
>50%	0.00%	0
25-50%	0.00%	0
10-25%	28.57%	2
<10%	71.43%	5
TOTAL		7

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: 8 Skipped: 1



ANSWER CHOICES	RESPONSES	
Yes	37.50%	3
No	62.50%	5
TOTAL		8

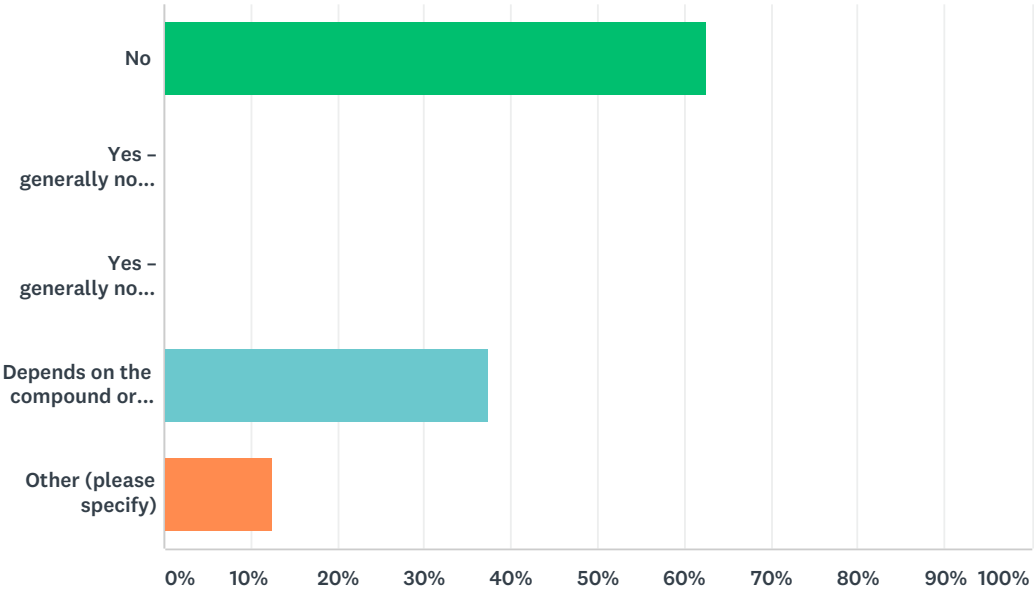
Q25 If you answered "Yes" to Question 24, please describe scenarios in which such tools may be used and what software is being used:

Answered: 4 Skipped: 5

#	RESPONSES	DATE
1	na	10/25/2019 1:27 PM
2	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 9:19 PM
3	SimCYP – simulate poor, normal and extensive metabolizers	10/10/2019 1:23 PM
4	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 1:38 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: 8 Skipped: 1

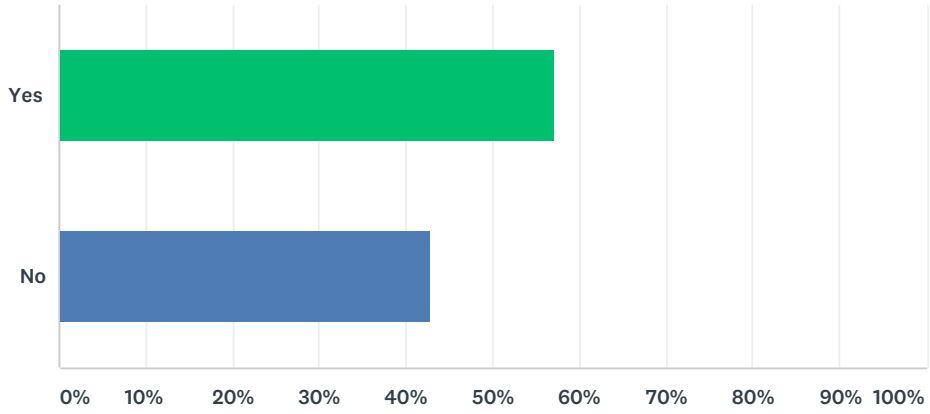


ANSWER CHOICES	RESPONSES	
No	62.50%	5
Yes – generally no progression with over 50% contribution of enzyme	0.00%	0
Yes – generally no progression with over 50% contribution of transporter	0.00%	0
Depends on the compound or therapeutic area (please describe further – fill in)	37.50%	3
Other (please specify)	12.50%	1
Total Respondents: 8		

#	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 9:19 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: 7 Skipped: 2



ANSWER CHOICES	RESPONSES	
Yes	57.14%	4
No	42.86%	3
TOTAL		7

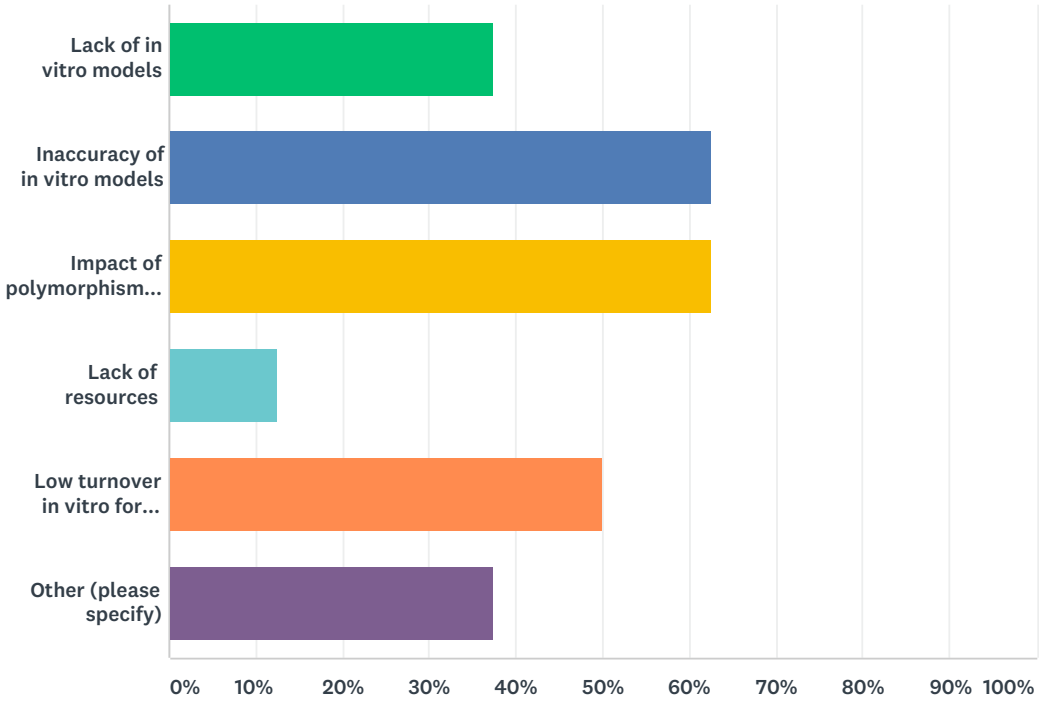
Q28 If you answered "Yes" to Question 27 please describe (e.g. use of genotyped hepatocytes, recombinant systems expressing variant. Please include specific enzymes/transporters and alleles assayed using a given method.)

Answered: 4 Skipped: 5

#	RESPONSES	DATE
1	major isozymes	10/25/2019 1:27 PM
2	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 9:19 PM
3	.) 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 1:23 PM
4	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 1:38 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: 8 Skipped: 1

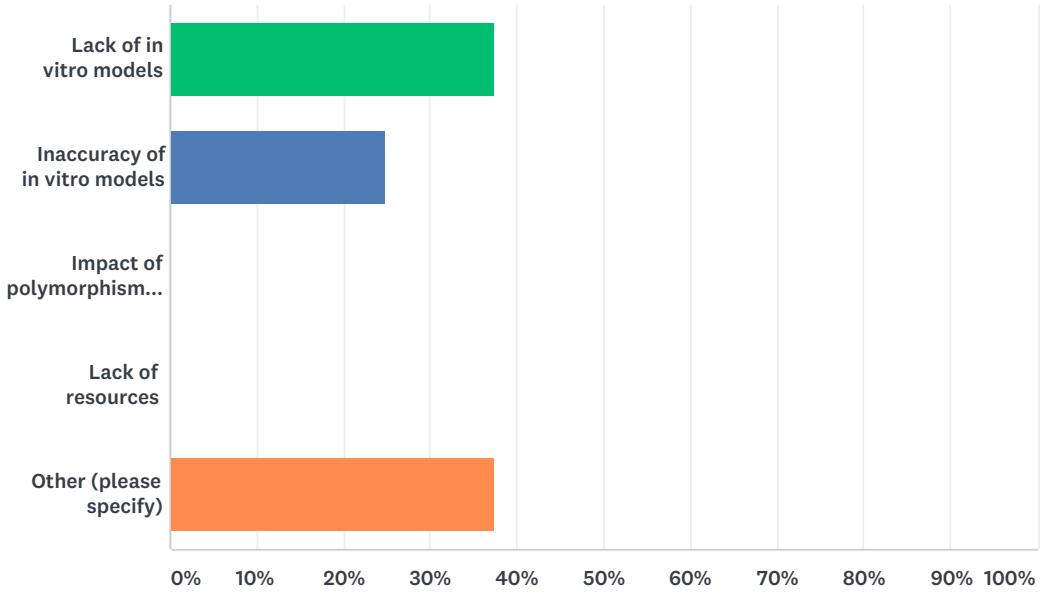


ANSWER CHOICES	RESPONSES	
Lack of in vitro models	37.50%	3
Inaccuracy of in vitro models	62.50%	5
Impact of polymorphisms is not well characterized	62.50%	5
Lack of resources	12.50%	1
Low turnover in vitro for certain compounds	50.00%	4
Other (please specify)	37.50%	3
Total Respondents: 8		

#	OTHER (PLEASE SPECIFY)	DATE
1	Scaling factors are not well characterized.	10/14/2019 9:22 PM
2	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 9:19 PM
3	combination of enzymes+transporters	10/10/2019 1:23 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: 8 Skipped: 1



ANSWER CHOICES	RESPONSES	
Lack of in vitro models	37.50%	3
Inaccuracy of in vitro models	25.00%	2
Impact of polymorphisms is not well characterized	0.00%	0
Lack of resources	0.00%	0
Other (please specify)	37.50%	3
TOTAL		8

#	OTHER (PLEASE SPECIFY)	DATE
1	Scaling factors are not well characterized.	10/14/2019 9:22 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 9:19 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 1:23 PM