#1

COMPLETE

Collector:	Email Invitation 1 (Email)
Started:	Wednesday, September 25, 2019 3:01:15 AM
Last Modified:	Wednesday, September 25, 2019 3:07:21 AM
Time Spent:	00:06:06
Email:	
IP Address:	

Page 1: ADME Task Force Survey

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

1744

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

Internal/proprietary data,

Literature search,

PharmGKB (https://www.pharmgkb.org/)

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:

Respondent skipped this question

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

Individual alleles or variants are tested

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:

Respondent skipped this question

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:

Respondent skipped this question

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:

Use in vitro experimental approaches to decipher the substrate-specific functionality and subsequently derive a predicted metabolic phenotype

,

Where possible, asses impact of individual variants as a part of genetic analyses in human studies

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?	**Respondent skipped this question**
Q9 Which of the following CYP2C19 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q10 Please select the CYP2D6 phenotype assignments based on allele functional status (diplotypes) below you agree with. Select all that apply:	**Respondent skipped this question**
Q11 If you did not agree with any of the assignments in Question 10, please describe why:	**Respondent skipped this question**
Q12 Which of the following CYP3A5 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q13 Which of the following UGT1A1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q14 Which of the following SLCO1B1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q15 Which of the following BCRP alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q16 Which of the following OCT1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q17 Do you believe design of a standard ADME PGx Reference Set as described above would be valuable for the field?	**Yes**
Q18 Please provide an explanation to for your response to Question 15:	**Respondent skipped this question**

Q19 Under what circumstances would you utilize an ADME PGx Reference Set at your company: Select all that apply	**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** **,** **Would genotype and analyze data for genes in panel where there is unexplained PK variability**
Q20 What possible challenges or limitations do you see in development or utility of an ADME Reference Set? Select all that apply:	**Will be very time consuming to develop**
Q21 To be useful, how often would an ADME PGx Reference Set need to be updated?	**Yearly**
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?	**Yes, this would be valuable**
Q23 Please provide any additional comments on this topic:	**Respondent skipped this question**

#2

COMPLETE

Collector: Email Invitation 1 (Email)
Started: Thursday, September 26, 2019 5:02:54 PM
Last Modified: Thursday, September 26, 2019 5:29:39 PM
Time Spent: 00:26:45
Email:
IP Address:

Page 1: ADME Task Force Survey

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

Respondent skipped this question

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

PharmGKB (https://www.pharmgkb.org/),

PharmVar (https://www.pharmvar.org/),

UGT Nomenclature Site (https://www.pharmacogenomics.pha.ulaval.ca/ugt-alleles-nomenclature/)

,

PGx guidelines from CPIC or DPWG **,**

Other (please specify):

UW DDI https://www.druginteractioninfo.org/

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:

Lack of transporter database.

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

Genotypes are classified into phenotypes (e.g. Extensive function, intermediate function, poor Function)

,

Individual alleles or variants are tested

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:

It just depends on whether this is a known way to call phenotype, if not, individual alleles are assessed as needed.

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:

External sources from list above using generally accepted nomenclature, no internal definitions are used.

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:

Other (please specify):

No, we report generic prediction and communicate caveats to clinical teams.

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?

***2,**

***3,**

Other (please specify):

We have looked at others, but given the frequency, *2 and *3 are routinely run.

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

***2,**

***3,**

***4,**

***5,**

***17,**

Other (please specify):

Same caveat as above, have looked at others, but routinely do not run due to frequency.

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

Normal/decreased function (i.e. *1/*10) is , EM

Normal/no function (i.e. *1/*4) is , IM

No/decreased function (i.e. *4/*41) is , IM

Increased/decreased function (i.e. *1xN/*17) is , EM

Increased/no function i.e. (*1xN/*4) is IM

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

We agree.

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

***3,**

***6,**

***7**

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

***6,**

***27,**

***28,**

***36,**

***37,**

Other (please specify):

We look at *60 routinely.

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

***5,**

***15,**

Other (please specify):

*1B routinely

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

rs2231142 (421C>A, Gln141Lys),

Other (please specify):

rs72552713 routinely

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

Arg61Cys,

Cys88Arg,

Gly401Ser,

Met420del,

Gly465Arg

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

Yes

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

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.

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

Where tools are available, would use reference set to guide preclinical work

,

Would genotype all Phase I clinical study subjects for alleles included in this set

,

Would conduct ADME PGx analyses for all alleles in the set in all phase I studies

,

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

,

Would genotype and analyze data for genes in panel where there is unexplained PK variability

---

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

Other (please specify):

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.

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

Every 2 Years

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?

Yes, this would be valuable, but in addition to a reference panel

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Q23 Please provide any additional comments on this topic:

With regard to question 21, if the panel is set up well to start, there won't be much new each year to add.

#3

COMPLETE

Collector: Email Invitation 1 (Email)
Started: Tuesday, October 01, 2019 3:19:57 PM
Last Modified: Tuesday, October 01, 2019 3:22:00 PM
Time Spent: 00:02:03
Email:
IP Address:

Page 1: ADME Task Force Survey

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

7345

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

Internal/proprietary data,

Literature search,

PharmVar (https://www.pharmvar.org/)

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:

NA

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

Other (please specify):

Not relevant to role

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:

N

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:

Respondent skipped this question

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:

Respondent skipped this question

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?	**Respondent skipped this question**
Q9 Which of the following CYP2C19 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q10 Please select the CYP2D6 phenotype assignments based on allele functional status (diplotypes) below you agree with. Select all that apply:	**Respondent skipped this question**
Q11 If you did not agree with any of the assignments in Question 10, please describe why:	**Respondent skipped this question**
Q12 Which of the following CYP3A5 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q13 Which of the following UGT1A1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q14 Which of the following SLCO1B1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q15 Which of the following BCRP alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q16 Which of the following OCT1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q17 Do you believe design of a standard ADME PGx Reference Set as described above would be valuable for the field?	**Respondent skipped this question**
Q18 Please provide an explanation to for your response to Question 15:	**Respondent skipped this question**

Q19 Under what circumstances would you utilize an ADME PGx Reference Set at your company: Select all that apply	**Respondent skipped this question**
Q20 What possible challenges or limitations do you see in development or utility of an ADME Reference Set? Select all that apply:	**Respondent skipped this question**
Q21 To be useful, how often would an ADME PGx Reference Set need to be updated?	**Respondent skipped this question**
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?	**Respondent skipped this question**
Q23 Please provide any additional comments on this topic:	**Respondent skipped this question**

#4

COMPLETE

Collector: Email Invitation 2 (Email)
Started: Friday, October 11, 2019 7:15:39 AM
Last Modified: Friday, October 11, 2019 8:07:04 AM
Time Spent: 00:51:24
Email:
IP Address:

Page 1: ADME Task Force Survey

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

7755

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

Literature search,

PharmGKB (https://www.pharmgkb.org/),

PharmVar (https://www.pharmvar.org/),

UGT Nomenclature Site (https://www.pharmacogenomics.pha.ulaval.ca/ugt-alleles-nomenclature/)

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:

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

Genotypes are classified into phenotypes (e.g. Extensive function, intermediate function, poor Function)

,

Individual alleles or variants are tested

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:

Approaches depend on which ADME genes are in question, clinically known/validate effect or whether the analysis in more exploratory research in nature

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:

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:	Other (please specify): NA
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?	**Respondent skipped this question**
Q9 Which of the following CYP2C19 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q10 Please select the CYP2D6 phenotype assignments based on allele functional status (diplotypes) below you agree with. Select all that apply:	**Respondent skipped this question**
Q11 If you did not agree with any of the assignments in Question 10, please describe why:	**Respondent skipped this question**
Q12 Which of the following CYP3A5 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q13 Which of the following UGT1A1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q14 Which of the following SLCO1B1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q15 Which of the following BCRP alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**

Q16 Which of the following OCT1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q17 Do you believe design of a standard ADME PGx Reference Set as described above would be valuable for the field?	**Yes**
Q18 Please provide an explanation to for your response to Question 15:	**Respondent skipped this question**
Q19 Under what circumstances would you utilize an ADME PGx Reference Set at your company: Select all that apply	**Where tools are available, would use reference set to guide preclinical work** **,** **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** **,** **Would genotype and analyze data for genes in panel where there is unexplained PK variability**
Q20 What possible challenges or limitations do you see in development or utility of an ADME Reference Set? Select all that apply:	**Current state of knowledge is rapidly evolving – will be challenging to keep a reference set up to date**
Q21 To be useful, how often would an ADME PGx Reference Set need to be updated?	**Yearly**
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?	**Yes, this would be valuable**
Q23 Please provide any additional comments on this topic:	**Respondent skipped this question**

#5

COMPLETE

Collector: Email Invitation 1 (Email)
Started: Friday, October 11, 2019 1:52:07 PM
Last Modified: Friday, October 11, 2019 1:58:04 PM
Time Spent: 00:05:56
Email:
IP Address:

Page 1: ADME Task Force Survey

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

3309

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

Internal/proprietary data,

Literature search,

PharmGKB (https://www.pharmgkb.org/),

PharmVar (https://www.pharmvar.org/),

PGx guidelines from CPIC or DPWG

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:

range of ethnicity and impact

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

Genotypes are classified into phenotypes (e.g. Extensive function, intermediate function, poor Function)

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:

Respondent skipped this question

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:

internal

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:	**Where possible, asses impact of individual variants as a part of genetic analyses in human studies**
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?	**Respondent skipped this question**
Q9 Which of the following CYP2C19 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q10 Please select the CYP2D6 phenotype assignments based on allele functional status (diplotypes) below you agree with. Select all that apply:	**Respondent skipped this question**
Q11 If you did not agree with any of the assignments in Question 10, please describe why:	**Respondent skipped this question**
Q12 Which of the following CYP3A5 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q13 Which of the following UGT1A1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q14 Which of the following SLCO1B1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q15 Which of the following BCRP alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**
Q16 Which of the following OCT1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Respondent skipped this question**

Q17 Do you believe design of a standard ADME PGx Reference Set as described above would be valuable for the field?	**Yes**
Q18 Please provide an explanation to for your response to Question 15:	**Respondent skipped this question**
Q19 Under what circumstances would you utilize an ADME PGx Reference Set at your company: Select all that apply	**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**
Q20 What possible challenges or limitations do you see in development or utility of an ADME Reference Set? Select all that apply:	**Will be difficult to find agreement across the field**
Q21 To be useful, how often would an ADME PGx Reference Set need to be updated?	**Every 2 Years**
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?	**Yes, this would be valuable**
Q23 Please provide any additional comments on this topic:	**Respondent skipped this question**

#6

COMPLETE

Collector: Email Invitation 1 (Email)
Started: Friday, October 11, 2019 9:33:54 PM
Last Modified: Friday, October 11, 2019 9:49:57 PM
Time Spent: 00:16:03
Email:
IP Address:

Page 1: ADME Task Force Survey

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

5351

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

Internal/proprietary data,

Literature search,

PharmGKB (https://www.pharmgkb.org/),

PharmVar (https://www.pharmvar.org/),

UGT Nomenclature Site (https://www.pharmacogenomics.pha.ulaval.ca/ugt-alleles-nomenclature/)

,

PGx guidelines from CPIC or DPWG

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:

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.

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

Genotypes are classified into phenotypes (e.g. Extensive function, intermediate function, poor Function)

,

Individual alleles or variants are tested

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:

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.

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:

Generally use definitions provided by PharmGKB/CPIC.

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:

Use in vitro experimental approaches to decipher the substrate-specific functionality and subsequently derive a predicted metabolic phenotype

,

Where possible, asses impact of individual variants as a part of genetic analyses in human studies

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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?

***2,**

***3,**

***4,**

***5,**

***6,**

***8,**

***11,**

***12,**

***13,**

***15,**

***25,**

***31**

Q9 Which of the following CYP2C19 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	***2,** ***3,** ***4,** ***5,** ***6,** ***7,** ***8,** ***9,** ***10,** ***16,** ***17,** ***19,** ***22,** ***24,** ***25,** ***26,** ***35**
Q10 Please select the CYP2D6 phenotype assignments based on allele functional status (diplotypes) below you agree with. Select all that apply:	**Respondent skipped this question**
Q11 If you did not agree with any of the assignments in Question 10, please describe why:	**Respondent skipped this question**
Q12 Which of the following CYP3A5 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	***3,** ***6,** ***7**
Q13 Which of the following UGT1A1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	***6,** ***27,** ***28,** ***36,** ***37,** ***80**

Q14 Which of the following SLCO1B1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	***5,** ***15,** ***17**
Q15 Which of the following BCRP alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**rs2231142 (421C>A, Gln141Lys)**
Q16 Which of the following OCT1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Arg61Cys,** **Cys88Arg,** **Gly401Ser,** **Met420del,** **Gly465Arg**
Q17 Do you believe design of a standard ADME PGx Reference Set as described above would be valuable for the field?	**No**

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

Useful in theory, but will be difficult to implement and substantial overlap with existing resources.

Q19 Under what circumstances would you utilize an ADME PGx Reference Set at your company: Select all that apply	Other (please specify): Would use to guide testing where inclusion or exclusion of subjects based on PGx genotype was required.
Q20 What possible challenges or limitations do you see in development or utility of an ADME Reference Set? Select all that apply:	**Will be difficult to find agreement across the field ,** **Current state of knowledge is rapidly evolving – will be challenging to keep a reference set up to date ,** **Too much overlap with other existing resources ,** **Will be very time consuming to develop**
Q21 To be useful, how often would an ADME PGx Reference Set need to be updated?	**Yearly**

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?

Yes, this would be valuable

Q23 Please provide any additional comments on this topic:

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.

#7

COMPLETE

Collector: Email Invitation 1 (Email)
Started: Monday, October 14, 2019 7:57:36 PM
Last Modified: Monday, October 14, 2019 8:53:21 PM
Time Spent: 00:55:44
Email:
IP Address:

Page 1: ADME Task Force Survey

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

2088

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

Internal/proprietary data,

Literature search,

PharmGKB (https://www.pharmgkb.org/),

PharmVar (https://www.pharmvar.org/),

UGT Nomenclature Site (https://www.pharmacogenomics.pha.ulaval.ca/ugt-alleles-nomenclature/)

,

ePKgene (http://gene.druginteractioninfo.org/) **,**

PGx guidelines from CPIC or DPWG

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:

. 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.

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

Genotypes are classified into phenotypes (e.g. Extensive function, intermediate function, poor Function)

,

Individual alleles or variants are tested

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:

. 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.

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:

Both internal definition and external definition are integrated for use.

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:

Use in vitro experimental approaches to decipher the substrate-specific functionality and subsequently derive a predicted metabolic phenotype

,

Where possible, asses impact of individual variants as a part of genetic analyses in human studies

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?

***2,**

***3,**

***5,**

***6,**

***11,**

***13**

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

***2,**

***3,**

***4,**

***5,**

***6,**

***7,**

***8,**

***17**

Q10 Please select the CYP2D6 phenotype assignments based on allele functional status (diplotypes) below you agree with. Select all that apply:	**Normal/decreased function (i.e. *1/*10) is EM ,** **Normal/no function (i.e. *1/*4) is IM ,** **No/decreased function (i.e. *4/*41) is IM**
Q11 If you did not agree with any of the assignments in Question 10, please describe why:	**Respondent skipped this question**
Q12 Which of the following CYP3A5 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	***3,** ***6**
Q13 Which of the following UGT1A1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	***6,** ***27,** ***28,** ***36,** ***37**
Q14 Which of the following SLCO1B1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	***5,** ***14,** ***15,** ***17,** Other (please specify): *4 and *21
Q15 Which of the following BCRP alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**rs2231142 (421C>A, Gln141Lys)**
Q16 Which of the following OCT1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	**Arg61Cys,** **Cys88Arg,** **Gly401Ser,** **Met420del,** **Gly465Arg**

Q17 Do you believe design of a standard ADME PGx Reference Set as described above would be valuable for the field?	**No**

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

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.

Q19 Under what circumstances would you utilize an ADME PGx Reference Set at your company: Select all that apply	**Would not utilize an ADME PGx Reference set**
Q20 What possible challenges or limitations do you see in development or utility of an ADME Reference Set? Select all that apply:	**Current state of knowledge is rapidly evolving – will be challenging to keep a reference set up to date** , **Too much overlap with other existing resources** , **Will be very time consuming to develop**
Q21 To be useful, how often would an ADME PGx Reference Set need to be updated?	**Yearly**
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?	**Yes, this would be valuable**
Q23 Please provide any additional comments on this topic:	**Respondent skipped this question**

#8

COMPLETE

Collector: Email Invitation 1 (Email)
Started: Tuesday, November 05, 2019 7:56:18 AM
Last Modified: Tuesday, November 05, 2019 8:04:35 AM
Time Spent: 00:08:17
Email:
IP Address:

Page 1: ADME Task Force Survey

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

7507

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

Internal/proprietary data,

Literature search,

PharmGKB (https://www.pharmgkb.org/),

PharmVar (https://www.pharmvar.org/),

UGT Nomenclature Site (https://www.pharmacogenomics.pha.ulaval.ca/ugt-alleles-nomenclature/)

,

ePKgene (http://gene.druginteractioninfo.org/) **,**

PGx guidelines from CPIC or DPWG

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:

transporter mediated disposition

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

Genotypes are classified into phenotypes (e.g. Extensive function, intermediate function, poor Function)

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:

N/A

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:

N/A

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:

Use in vitro experimental approaches to decipher the substrate-specific functionality and subsequently derive a predicted metabolic phenotype

,

Where possible, asses impact of individual variants as a part of genetic analyses in human studies

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?

Other (please specify):

N/A

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

Other (please specify):

N/A

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

Normal/decreased function (i.e. *1/*10) is EM

,

Normal/no function (i.e. *1/*4) is IM

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

N/A

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

***3,**

***6**

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

***6,**

***27**

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

Other (please specify):

N/A

Q15 Which of the following BCRP alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	Other (please specify): N/A
Q16 Which of the following OCT1 alleles do you consider to affect (increase or decrease) enzyme or transporter activity?	Other (please specify): N/A
Q17 Do you believe design of a standard ADME PGx Reference Set as described above would be valuable for the field?	**Yes**

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

Would allow to interprete the disposition profilie with variants relating to PG

Q19 Under what circumstances would you utilize an ADME PGx Reference Set at your company: Select all that apply	**Would genotype and analyze data for genes in panel where there is unexplained PK variability**
Q20 What possible challenges or limitations do you see in development or utility of an ADME Reference Set? Select all that apply:	Other (please specify): Acceptability by regulatory agencies when it comes to interpretation of NCE in submission dossier
Q21 To be useful, how often would an ADME PGx Reference Set need to be updated?	**Every 3-5 Years**
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?	**Yes, this would be valuable, but in addition to a reference panel**
Q23 Please provide any additional comments on this topic:	**Respondent skipped this question**