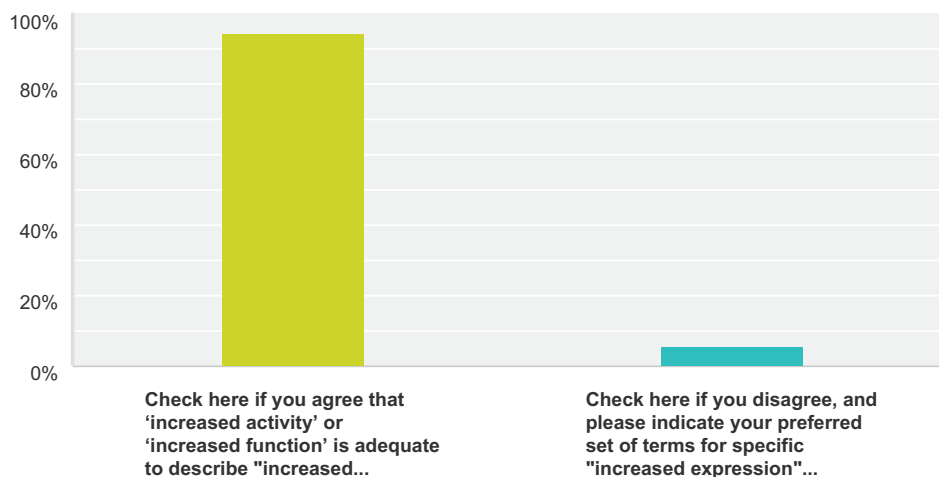


Q1 We recognize that no set of terms will be ideal for all alleles. For example, the terms “function” and “activity” are not technically accurate when the variant affects the amount of protein expressed versus altering the protein function/activity via inactivating variants. However, the ultimate clinical consequence is that there is greater “function” or greater “activity,” so from a clinical standpoint, this distinction may not be necessary and might lead to confusion among clinicians and patients. Please read this statement, "The consensus seems to be that translating, for example, a CYP2C19*17 allele and an extra copy (e.g. n = 3 or 4 copies) of CYP2D6*1 into the interpretation 'increased activity' or 'increased function' is adequate, rather than a more detailed interpretation such as 'increased expression of active protein,' 'increased transcript level' or 'extra copy of functional gene.'"

Answered: 54 Skipped: 0



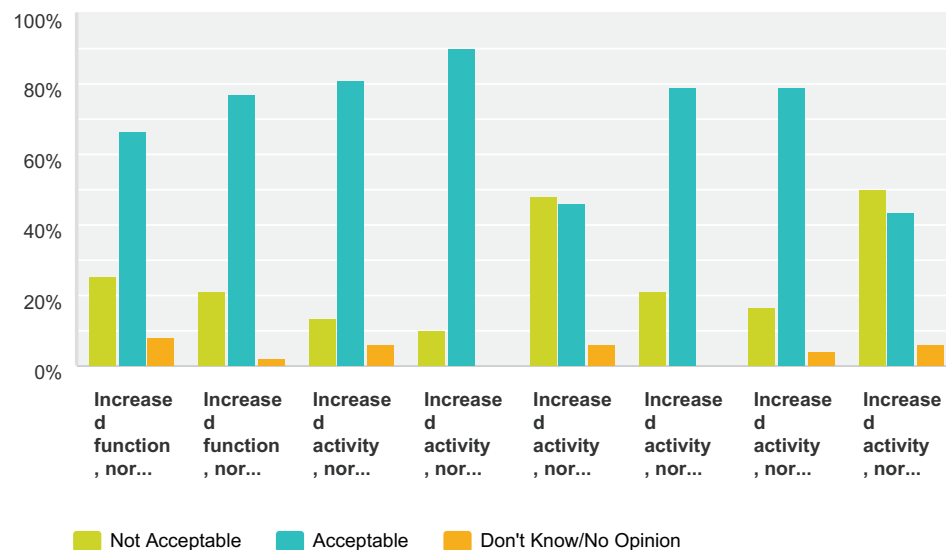
Answer Choices	Responses
Check here if you agree that 'increased activity' or 'increased function' is adequate to describe "increased expression" genes/alleles	94.44% 51
Check here if you disagree, and please indicate your preferred set of terms for specific "increased expression" genes/alleles	5.56% 3
Total	54

CPIC Term Standardization for Clinical Pharmacogenetic Test Results: alleles and phenotypes-Delphi 2

#	Check here if you disagree, and please indicate your preferred set of terms for specific "increased expression" genes/alleles	Date
1	<p>There is a difference between making an assertion about the functional status of an allele and the overall phenotype for a given gene. I think we should keep these assertions clearly separated since they describe different steps in the translation from genotype to system-level phenotype. For example, if one allele resulted in increased expression of a "normal function" enzyme, another allele resulted in reduced enzymatic function (but normal expression), and the diplotype combination of the two was functionally "normal", I think we would want the ability to record all three of those assertions. Only the last might be shown to a clinician, but we shouldn't skip the intermediate steps. Once data is lost it is very hard to re-create. We should have terms to support each step in the translation process.</p>	4/17/2015 9:29 AM
2	Increased expression of active protein.	4/14/2015 1:46 PM
3	<p>I disagree that increased activity OR increased function are adequate to describe increased expression. I do agree that increased activity is more technically accurate and I believe should satisfy the definition from a clinical standpoint.</p>	4/9/2015 12:25 PM

Q2 On the first survey (Delphi 1), experts agreed that the same sets of terms could be used to describe allele functional status for the genes coding for drug metabolizing enzymes. Therefore, this question pertains to DPYD, TPMT, CYP2C19, CYP2C9, CYP2D6, CYP3A5, and UGT1A1 (see table below for examples of possible alleles for the 4 different categories for each gene). Please indicate your acceptance of EACH set of terms below used to describe allele functional status. If you choose “not acceptable,” please explain why you do not think these terms are acceptable. You may also comment about acceptable terms:

Answered: 54 Skipped: 0



	Not Acceptable	Acceptable	Don't Know/No Opinion	Total	Weighted Average
Increased function, normal function, reduced function, no function	25.49% 13	66.67% 34	7.84% 4	51	1.72
Increased function, normal function, reduced function, non-functional	21.15% 11	76.92% 40	1.92% 1	52	1.78
Increased activity, normal activity, reduced activity, no activity	13.46% 7	80.77% 42	5.77% 3	52	1.86
Increased activity, normal activity, decreased activity, no activity	9.80% 5	90.20% 46	0.00% 0	51	1.90
Increased activity, normal activity, intermediate activity, no activity	47.92% 23	45.83% 22	6.25% 3	48	1.49

CPIC Term Standardization for Clinical Pharmacogenetic Test Results: alleles and phenotypes-Delphi 2

Increased activity, normal activity, reduced activity, inactive	20.83% 10	79.17% 38	0.00% 0	48	1.79
Increased activity, normal activity, decreased activity, inactive	16.67% 8	79.17% 38	4.17% 2	48	1.83
Increased activity, normal activity, intermediate activity, inactive	50.00% 24	43.75% 21	6.25% 3	48	1.47

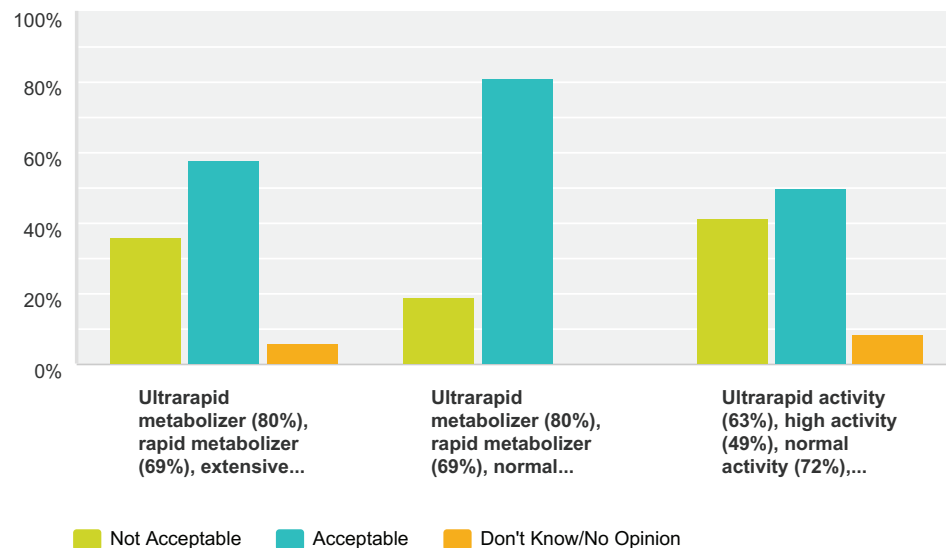
#	If you chose not acceptable, please explain which terms you think are not acceptable and why. You may also comment about acceptable terms:	Date
1	1. probably a minor semantic point, but I would not use "non-functional" because it is different formatting from "increased/normal/reduced FUNCTION" 2. "intermediate" activity is likely to be too vague to be clinically useful	4/24/2015 4:14 PM
2	"Decreased" is a more natural pair for "increased" than is "reduced". I would have preferred to see an option for increased/decreased function. I do not like having a term for "intermediate" without also having a term for "reduced" or "decreased". I think the phenotypic range of activity is too large to go from intermediate to none.	4/17/2015 9:33 AM
3	Intermediate Activity doesn't seem to convey the same as decreased activity or reduced activity. In the example provided below for CYP3A5 - *3 is non functional allele and *1 is normal functional allele.	4/15/2015 1:44 PM
4	Not a fan of "intermediate" since I don't think you can judge based on that word whether the activity is greater or less than "normal". I think that using "no function" and "no activity" are more consistent word choices than "non-functional" or "inactive", but I don't think this is very important.	4/14/2015 2:35 PM
5	The term intermediate when there are 4 categories is unclear. It is not intuitive to those outside of the PGx world to know that intermediate lies between inactive and normal, and not between normal and increased.	4/14/2015 1:48 PM
6	The term intermediate activity leaves too much room for confusion and should be avoided	4/13/2015 5:36 PM
7	In previous surveys, our physicians reported disliking the term "intermediate" due to its ambiguity (i.e. "intermediate relative to what?")	4/13/2015 2:11 PM
8	I think "intermediate" can be mistakenly understood as "normal" without context because "intermediate" sounds like "average." The Merriam-Webster dictionary definition of "intermediate" is "being or occurring at the middle place, stage, or degree or between extremes," which should mean it has average activity, but in this case it is actually referring to reduced activity. If a clinician is given a patient's report that only says "intermediate activity," they may think it is normal or average, when in fact it is actually decreased/reduced. "Intermediate" only makes sense when it is given in context of the alternatives.	4/13/2015 12:58 PM
9	I prefer the use of activity because I think we have to focus on the drug clearance. I believe that we will eventually be able to detect constitutive changes in activity based on interactive endogenous effects. Function from my point of view has a greater reference to the enzyme rather than the drug. However, in the long run consistency is more important whichever way the group decides.	4/13/2015 10:12 AM
10	no function is probably not correct -- these variants may still have a function. (the table below the text box contained an error -- CYP3A5*1 is a gain-of-function allele and not a inactive one)	4/12/2015 8:28 AM
11	I prefer the term reduced over intermediate in the context of the other adjectives. AS for reduced vs decreased, I am OK with both of them. I also prefer the term "inactive allele" rather than "no activity allele," only because it flows better in a sentence.	4/10/2015 10:37 AM
12	In the table below there is a typo: CYP3A5*1 is "Normal" and CYP3A5*3 is "No/Inactive/nonfunctional". "Decreased" is better than "reduced" because then we can use increased (the opposite of decreased). "Intermediate" does not imply directionality the same way that "decreased" does. Prefer "no activity" rather than "inactive" because then all the descriptions are using a modifier of "activity" rather than a different set of terms. In general, consistency in terminology is preferred.	4/9/2015 3:23 PM
13	No function is such an absolute ... what if detection methods indicate in the future that an allele currently designated as no function is actually deleterious or inhibitory to the true function. Intermediate activity is too vague.	4/9/2015 2:01 PM
14	I think "inactive" is a little vague. Also think "activity" is more clear than "function"	4/9/2015 1:32 PM
15	I prefer the term "activity" to describe alleles in relation to other alleles because sometimes alleles are functional but have decreased expression.	4/9/2015 12:30 PM

CPIC Term Standardization for Clinical Pharmacogenetic Test Results: alleles and phenotypes-Delphi 2

16	Function vs activity = either is fine but if pressed I would choose 'activity' b/c the enzymes in question are performing an action on a substrate maybe more than they are a function on a substrate. no function does not seem to be an adjective as much as 'non-functional' (increased function allele sounds fine, non-functional allele sounds fine, no function allele seems to be missing the adjective aspect of the descriptor).	4/8/2015 10:44 AM
17	Intermediate activity is confusing because it sounds similar to Intermediate Metabolizer. Having a single decreased function (intermediate activity) allele does not always indicate Intermediate Metabolizer as a phenotype.	4/6/2015 1:01 PM
18	All terms appear acceptable. However, I am concerned that for the term intermediate it may be confusing to some.	4/2/2015 12:05 PM
19	do not like the term 'inactive' reduced and decreased are more accurately reflecting the activity of such alleles compared to intermediate.	4/2/2015 7:11 AM
20	The terms non-functional, inactive and intermediate are less clear than no function, no activity and decreased (reduced) function (activity).	4/1/2015 12:35 PM
21	I think intermediate and normal could be confused so I prefer reduced or decreased.	4/1/2015 9:54 AM
22	Not crazy about "no function"	3/31/2015 1:29 PM
23	The word "intermediate" conveys a message that "it's OK" when that is generally incorrect.	3/29/2015 2:33 PM
24	The term "inactive" may clinically imply there is something that can activate the enzyme. The term "intermediate activity" does not adequately convey to patients the activity level of the enzyme is lower or reduced.	3/27/2015 9:46 AM
25	While likely not discrete, allele function is perceived as more discrete than activity, i.e., activity is more of a continuum if you will. For all uses of "activity" relative to genes/alleles, "Not Acceptable" was chosen. If we can consistently use "function" for the genes/alleles, and "activity" for the product (DME), it will be clear what is being addressed in the literature and will be clear when reporting results.	3/26/2015 10:04 PM
26	If the goal is easy interpretation by physicians, I think that "activity" is a better description than "function" because it refers specifically to the amount of action rather than what could be misconstrued as a different type of action. I also don't like to use the term "normal" when referring to polymorphic loci in human genetics. If there's not a distinct pathogenic effect to a particular variation, and it's a widespread variation, who's to say what "normal" is? It's like saying a particular ethnic group has a "normal" level of skin pigmentation. I realize that the term could ease interpretation for physicians, but it may also provide more footing for the widespread public distrust of genetic testing. For this reason, I prefer "Reference activity," or "Reference-level activity," referring to the testing lab's reference genome.	3/26/2015 1:02 PM
27	intermediate is intermediate between what? like decreased or reduced better.	3/26/2015 9:36 AM
28	decreased and reduced activity/function are more likely to be confused with no activity/function.	3/25/2015 3:57 PM

Q3 Please indicate your acceptance of EACH set of terms below used to describe CYP2D6/CYP2C19/CYP2C9/CYP3A5 phenotypes. The percentage reported after each term indicates the percentage of experts from Delphi 1 who agreed or strongly agreed to that term (see table below for examples of possible diplotypes for the 4-5 different categories for each gene). If you choose “not acceptable,” please explain why you do not think these terms are acceptable. You may also comment about acceptable terms:

Answered: 53 Skipped: 1



	Not Acceptable	Acceptable	Don't Know/No Opinion	Total	Weighted Average
Ultrarapid metabolizer (80%), rapid metabolizer (69%), extensive (normal) metabolizer (62%), intermediate metabolizer (73%), poor metabolizer (70%)	36.00% 18	58.00% 29	6.00% 3	50	1.62
Ultrarapid metabolizer (80%), rapid metabolizer (69%), normal metabolizer (added based on Delphi 1 results), intermediate metabolizer (73%), poor metabolizer (70%)	18.87% 10	81.13% 43	0.00% 0	53	1.81
Ultrarapid activity (63%), high activity (49%), normal activity (72%), intermediate activity (62%), no activity (69%)	41.67% 20	50.00% 24	8.33% 4	48	1.55

#	If you chose not acceptable, please explain which terms you think are not acceptable and why. You may also comment about acceptable terms:	Date
1	"extensive (normal)" is technically correct, but likely to be confusing to many clinicians "high activity" is likely to be difficult to distinguish from ultrarapid and intermediate for many clinicians.	4/24/2015 4:21 PM

CPIC Term Standardization for Clinical Pharmacogenetic Test Results: alleles and phenotypes-Delphi 2

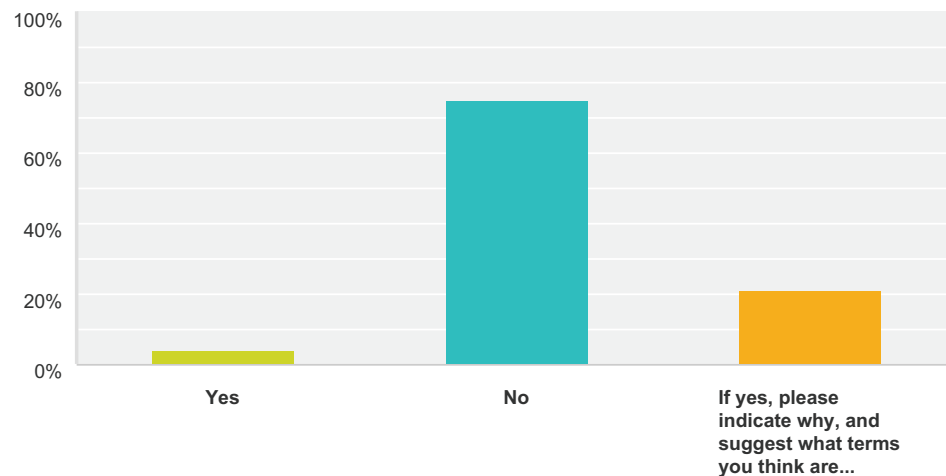
2	For CYP DME Metabolizer term seems more appropriate. Extensive Metabolizer - most individuals have a normal (extensive) metabolizer (EM) phenotype. But this term has been causing some confusion to clinicians. Normal Metabolizer fits in better. Isn't CPIC CYP2C19 *1/*17 Ultra Rapid Metabolizer category?	4/15/2015 1:46 PM
3	Extensive and normal metabolizer do not imply the same thing.	4/14/2015 10:13 PM
4	Again, really not sure about "intermediate", since I don't think it gives a clear enough idea whether this is above or below "normal" or "extensive" in activity. Why not have below-normal, reduced etc. metabolizer? Excluding this problem, I think the "ultrarapid metabolizer, rapid metabolizer, normal metabolizer, intermediate metabolizer, poor metabolizer" is the best choice.	4/14/2015 2:39 PM
5	The term "enzymatic activity" (with its corresponding units, ranges, etc) has been the term of choice in clinical chemistry. This applies to a multitude of enzymes. The same term should be used for specific DMEs providing there is a standardized assay to measure activity,	4/14/2015 2:22 PM
6	Although a standard term, the use of "intermediate" for a 4 category structure leads to confusion.	4/14/2015 1:54 PM
7	When talking to patients about their phenotype, they seem to understand they metabolize medication like food, etc. but activity is a more difficult concept to understand.	4/13/2015 5:36 PM
8	Not enough distinction between ultra rapid and high activity terms.	4/13/2015 4:19 PM
9	We do not think "extensive" should be used on its own.	4/13/2015 2:11 PM
10	Please see my previous comments on using "intermediate." I think it would be more appropriate to use "reduced" or "decreased" because "intermediate" can be mistakenly thought of as "average" or "normal" when it is not reported in context with the other options. [Sorry if this has changed since my first survey and created more work for you. I've had some more time to reflect on it since the first survey]	4/13/2015 1:12 PM
11	I would just go with the consensus to expedite the decision. Adding extensive (normal) adds more text and will lead to a potential for different descriptions.	4/13/2015 10:20 AM
12	Maybe we should move away from the term extensive since it can lead to confusion in clinicians who are not well versed in pharmacogenetics. Also, I prefer metabolizer status over activity because this is the function of these enzymes.	4/10/2015 11:12 AM
13	I think having both normal and intermediate is confusing. Intermediate should like they are normal. Slow or low is a better term.	4/9/2015 3:39 PM
14	The problem with "metabolizer" is that it only applies to enzymes (example VKORC1). If "activity" was used then we would need a different term for the allele ---- we prefer function/cellular phenotype/or even cellular activity. We prefer a consistent terminology across all PGx genes, but perhaps that isn't an option here. Oppose the term "intermediate" because it doesn't imply directionality. Oppose using "extensive" since it doesn't describe where on the spectrum some is - is it higher than rapid? or lower? (confusing for non-experts). Would be OK with ultrarapid, rapid, normal, decreased, poor metabolizer.	4/9/2015 3:29 PM
15	Extensive is too vague - most clinicians at our practice do not associate extensive with normal (they think upregulation).	4/9/2015 2:02 PM
16	"Metabolizer" is too jargon-y.	4/9/2015 1:34 PM
17	I believe 'activity' should be reserved to allele status definitions, not phenotype predictions.	4/9/2015 11:38 AM
18	The term "extensive" metabolizer can be misleading. If you need to clarify this term with "normal" in parentheses, you might as well just use "normal metabolizer."	4/8/2015 5:18 PM
19	The use of 'extensive' may mislead the understanding the semantics compare to normal. It's better to keep 'normal' instead of 'extensive' to avoid confusion.	4/8/2015 12:38 PM
20	Metabolizer seems to attribute the phenotype to the person. Someone is an ultrarapid metabolizer of a medication. A person is not an ultrarapid activity. So what may be helpful is considering the clinical context in how/who the descriptor will be used. Also, while 'ultrarapid' is something we have all grown up with, it may be useful in thinking about whether/how/when we can really distinguish (or where it is useful to distinguish) between rapid/ultrarapid - put another way is 'extra fast' different than just being 'fast' in the drug metabolism sense? I use ultrarapid in conversation and writing but thinking about whether this is worth doing. "Extensive" metabolizer is also a descriptor that we all use but in the clinical context have to clarify that this is 'normal'. Does a rapid metabolizer not also extensively metabolize a substrate? This may be worth thinking about as well.	4/8/2015 11:08 AM

CPIC Term Standardization for Clinical Pharmacogenetic Test Results: alleles and phenotypes-Delphi 2

21	We need to keep in mind that there are health care providers who are using pharmacogenetic testing who are now comfortable with the traditional metabolizer status phenotypes. Introducing a new set of 'activity' phenotypes, even though they may be more intuitive, may make it harder for these HCPs to interpret test results. Many of the HCPs who are using pharmacogenetic testing with current metabolizer phenotypes are talking to their less 'sophisticated' counterparts about the benefits of PGX. This is an important part of clinical implementation, and I would suggest we do not interfere with this process by putting in new terms.	4/6/2015 1:08 PM
22	Based on my clinical experience, clinicians do not understand what 'extensive' refers to and find the term confusing. If you have to define extensive by including (normal), it may be better to simplify and use normal. The meaning of high activity is unclear. Although I personally prefer intermediate, is there potential for confusion for those who are not experts in the field of PGx? If 4 other phenotypes are present (e.g., UM, rapid, normal, PM), it may be confusing to some where intermediate fits in. Was the term reduced (e.g., reduced activity) considered?	4/2/2015 12:15 PM
23	do not like the dual description of 'extensive (normal)' the term 'activity' may be preferable when talking to patients/nonprofessionals	4/2/2015 7:19 AM
24	Only one term should be used for normal, rapid and extensive metabolizers. All three questions include alternate terms for these metabolizers. I do not favour using "activity" for phenotypes. I do not think that activity is a good term for separating phenotypes; however for TMPT and DYPD you do not offer the use of "metabolizers". I suggest that the same terms should be used for all phenotypes , i.e., either "metabolizers" (which I favour) or "activity"	4/1/2015 12:45 PM
25	"Metabolizer" sounds like you're talking about a patient, not a phenotype for an allele. There are other characteristics that influence metabolism (age, weight), so I think it's better to make the term specific to the allele phenotype and not the patient. I understand these terms have been used for many years and clinicians are used to them though.	4/1/2015 10:01 AM
26	I prefer "metabolizer" versus "activity."	3/31/2015 1:34 PM
27	Again, the word "intermediate" is misleading.	3/29/2015 2:34 PM
28	Intermediate activity is difficult for patients to understand from my experience.	3/27/2015 9:54 AM
29	At this point there is a need to be clear relative to extensive/normal. Clinicians may ask "Is "extensive" "normal"?" However, it is unlikely they will ask "Is "normal" "extensive"?" Normal seems to be less ambiguous.	3/26/2015 10:13 PM
30	I'd argue against the use of the word "normal," as outlined in question 2.	3/26/2015 1:13 PM
31	I think that metabolizer status is common nomenclature; to change it to activity may confuse people.	3/26/2015 9:39 AM
32	Confusion may exist for CYP3A5- "normal metabolism" redefined to rapid metabolism etc.	3/26/2015 8:54 AM
33	activity used used to describe both enzyme and patient could confuse	3/25/2015 4:11 PM

Q4 For CYP3A5, very few terms met the 70% cut-off. Because some experts recommend that all CYP enzymes should have the same terms used to describe phenotypes, we grouped CYP3A5 with the other CYPs above. Do you think there should be different set of phenotype terms for CYP3A5 than for other CYPs?

Answered: 52 Skipped: 2



Answer Choices	Responses
Yes	3.85% 2
No	75.00% 39
If yes, please indicate why, and suggest what terms you think are appropriate for the 3 CYP3A5 phenotypes?	21.15% 11
Total	52

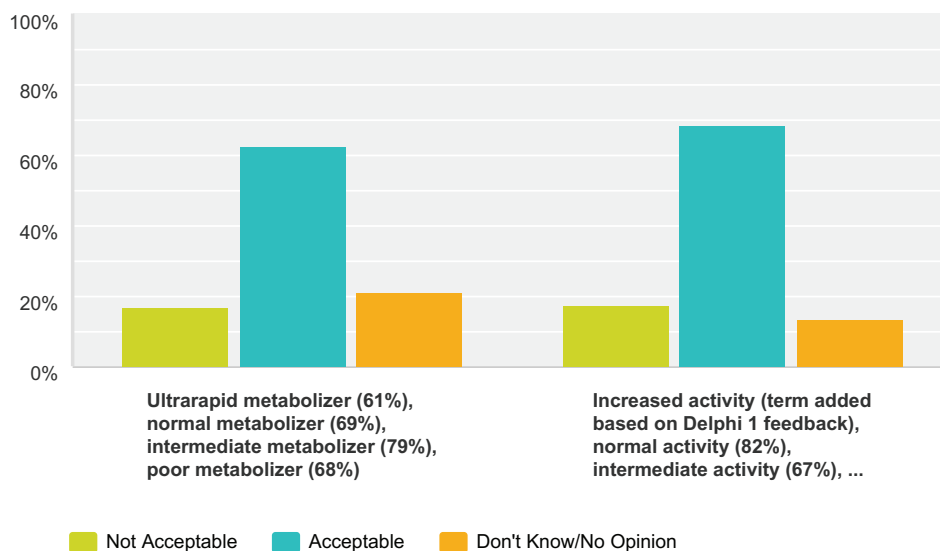
#	If yes, please indicate why, and suggest what terms you think are appropriate for the 3 CYP3A5 phenotypes?	Date
1	I'm not sure there needs to be different set of phenotype terms. The nuance has largely to do with the overlapping activities of 3A4 and 3A5. From a pure assessment of enzyme activity, I see no reason to use different terminology from the other CYP enzymes. For a specific 3A5-drug pair, the phenotypic assessment may vary with both the specific drug and the 3A4 status (as well as other genes). Perhaps the solution is to keep the same terminology for 3A5, but to strongly recommend tailored gene-drug pair reports that provide a greater degree of clinical guidance than a single enzyme report.	4/24/2015 4:21 PM
2	There e is a problem with 3A5 though, because some people believe 3A5 *3/*3 shoe should be WT as it is the predominat genotype, although it exhibits an impaired phenobype	4/14/2015 10:13 PM
3	*1/*1: normal activity, *1/*2: low activity, and *3/*3: no activity.	4/14/2015 2:22 PM
4	Metabolizer status is insufficient on its own; an additional term (such as "responder") would be required for adequate clinical interpretation. For example, a poor metabolizer would need to be noted at as "normal responder" for clinical interpretation.	4/13/2015 2:11 PM

CPIC Term Standardization for Clinical Pharmacogenetic Test Results: alleles and phenotypes-Delphi 2

5	I think that it will be confusing if we link this with CYP3A4 and handle it differently from the other enzymes; if you use the term CYP3A4/3A5, then you can use the terms listed above.	4/13/2015 10:20 AM
6	the problem with CYP3A5 is that by contrast to the other CYPs the most frequent allele, CYP3A5*3 is a no-activity allele. phenotype names should be similar to CYP2C19*17: CYP3A5*3/*3 : extensive/normal/ etc CYP3A5*1/*3: rapid metab CYP3A5*1/*1: ultrarapid	4/12/2015 8:34 AM
7	I might be the only one recommending this but why not do something different with CYP3A5: *3/*3 genotypes can be assigned an EM phenotype and *1/*1 patients have a UM phenotype. It will be easier for clinicians to understand that a UM phenotype is an actionable phenotype over the fact that a PM phenotype for CYP3A5 is not a high-risk phenotype but the EM phenotype is. These comment's are Cyrine's, please feel free to discuss them with her further.	4/10/2015 11:12 AM
8	Because 3A4/5 are not highly polymorphic, whereas the others listed are, and due to the fact they are so highly inducible and inhibited, it would be misleading to clinically relay an activity level without having terminology to also imply what affects the activity or expression.	3/27/2015 9:54 AM
9	CYP3A5 is polymorphic in a very different fashion than most CYPs. An interpretation of "poor" or "no activity" could be alarming to physicians and patients, when it is actually a very common situation. I'd prefer "expressor," "non-expressor," and "heterozygous expressor," if only to emphasize the difference. Actually, the same set of descriptors would be ideal, but only if physicians are well-educated about the results, which is unexpectedly difficult to accomplish (from the viewpoint of a clinical lab service provider).	3/26/2015 1:13 PM
10	redefinition of "normal metabolism"	3/26/2015 8:54 AM
11	Because of the allele frequencies with CYP3A5 polymorphisms, it may be difficult to define what is "normal"	3/25/2015 4:11 PM

Q5 Please indicate your acceptance of EACH set of terms below used to describe UGT1A1 phenotype. The percentage reported after each term indicates the percentage of experts from Delphi 1 who agreed or strongly agreed to that term (see table below for examples of possible diplotypes for the 4 different categories for the gene). If you choose “not acceptable,” please explain why you do not think these terms are acceptable. You may also comment about acceptable terms:

Answered: 54 Skipped: 0



	Not Acceptable	Acceptable	Don't Know/No Opinion	Total	Weighted Average
Ultrarapid metabolizer (61%), normal metabolizer (69%), intermediate metabolizer (79%), poor metabolizer (68%)	16.98% 9	62.26% 33	20.75% 11	53	1.79
Increased activity (term added based on Delphi 1 feedback), normal activity (82%), intermediate activity (67%), low activity (54%)	17.65% 9	68.63% 35	13.73% 7	51	1.80

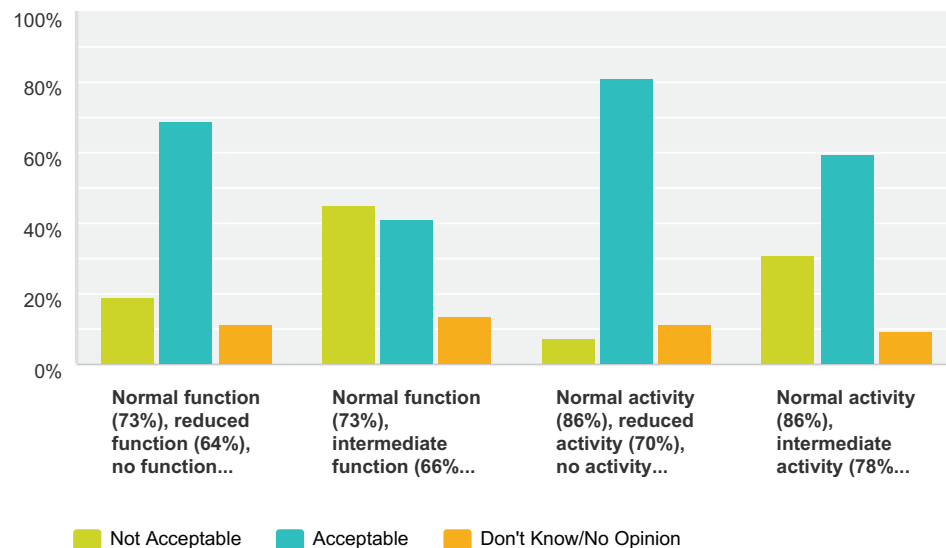
#	If you chose not acceptable, please explain which terms you think are not acceptable and why. You may also comment about acceptable terms:	Date
1	Slight preference for keeping the same terminology for this gene as for the CYP and other genes, so that clinicians less familiar with pharmacogenetics are not frustrated by variable terminology unless absolutely necessary.	4/24/2015 4:24 PM
2	Again, don't think "intermediate" is a good word choice. What about reduced or below-normal instead? Excluding this problem, I prefer the second option "increased activity, normal activity, intermediate activity, low activity".	4/14/2015 2:44 PM

CPIC Term Standardization for Clinical Pharmacogenetic Test Results: alleles and phenotypes-Delphi 2

3	Again, "activity" seems to be term of choice when referring to enzymes in clinical chemistry, providing there is a standardized assay to measure enzymatic activity for a given substrate.	4/14/2015 2:25 PM
4	We do not agree with the term "intermediate," which our clinicians have told us they do not understand. We find both metabolizer or activity acceptable.	4/13/2015 2:11 PM
5	See previous comments on use of "intermediate"	4/13/2015 1:12 PM
6	UGT1A1's function has historically been referred by a functional status. I personally believe that this nomenclature should be kept for UGT1A1 as opposed to changing it to a metabolizer status.	4/10/2015 11:21 AM
7	Same comments regarding intermediate as in the last question.	4/9/2015 3:40 PM
8	It is confusing to not use "rapid" metabolizer like the CYP genes. In addition, why not use the term "increased" for the CYP genes instead of rapid? These terms are qualitative terms in a particular order, skipping a term doesn't make sense. Opposed to using "intermediate" because it doesn't imply directionality.	4/9/2015 3:33 PM
9	"Metabolizer" is too jargon-y.	4/9/2015 1:34 PM
10	Per previous comments, should reduced/decreased activity be considered?	4/2/2015 12:17 PM
11	I do not think that activity is a good term for separating phenotypes;however for TMPT and DYPD you do not offer the use of "metabolizers". I suggest that the same terms should be used for all phenotypes , i.e., either "metabolizers" or "activity"	4/1/2015 12:45 PM
12	"Metabolizer" sounds like you're talking about a patient, not a phenotype for an allele. There are other characteristics that influence metabolism (age, weight), so I think it's better to make the term specific to the allele phenotype and not the patient.	4/1/2015 10:01 AM
13	see previous comment	3/29/2015 2:35 PM
14	I'd argue against the use of the word "normal," as outlined in question 2.	3/26/2015 1:14 PM
15	while technically correct to sue activit5y, it is better to use one nomenclature for all.	3/26/2015 9:41 AM

Q6 Please indicate your acceptance of EACH set of terms below used to describe DPYD or TPMT phenotype. The percentage reported after each term indicates the percentage of experts from Delphi 1 who agreed or strongly agreed to that term (see table below for examples of possible alleles for the 4 different categories for each gene). If you choose “not acceptable,” please explain why you do not think these terms are acceptable. You may also comment about acceptable terms:

Answered: 54 Skipped: 0



	Not Acceptable	Acceptable	Don't Know/No Opinion	Total	Weighted Average
Normal function (73%), reduced function (64%), no function (70%)	19.23% 10	69.23% 36	11.54% 6	52	1.78
Normal function (73%), intermediate function (66%), no function (70%)	45.10% 23	41.18% 21	13.73% 7	51	1.48
Normal activity (86%), reduced activity (70%), no activity (86%)	7.69% 4	80.77% 42	11.54% 6	52	1.91
Normal activity (86%), intermediate activity (78%), no activity (86%)	30.77% 16	59.62% 31	9.62% 5	52	1.66

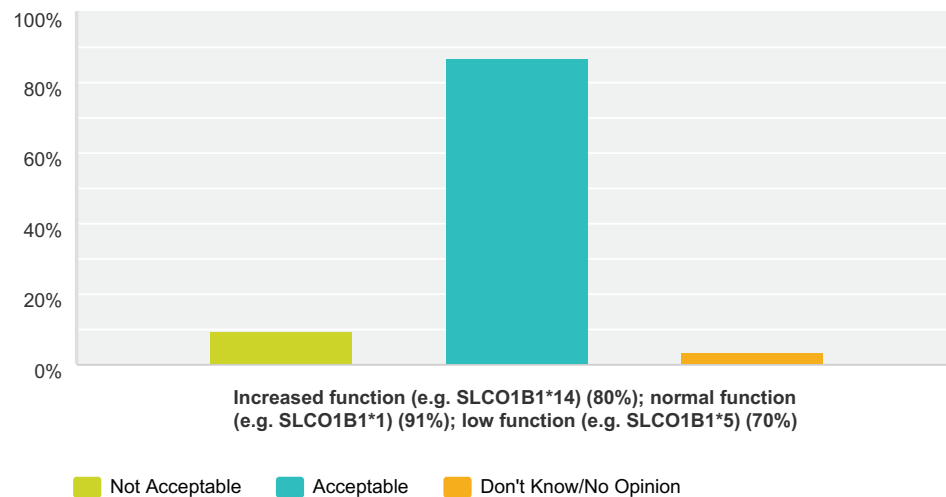
#	If you chose not acceptable, please explain which terms you think are not acceptable and why. You may also comment about acceptable terms:	Date

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1	Slight preference for "reduced" over "intermediate. As stated in prior comment, I also prefer to be as consistent as possible across all alleles and phenotypes with terminology--pick "function" or "activity" and stick with the same term everywhere.	4/24/2015 4:26 PM
2	I think "intermediate" implies a lower range other than "none", so I prefer the options that include "reduced".	4/17/2015 9:37 AM
3	Don't like "intermediate" but ambivalent regarding function vs activity.	4/14/2015 2:44 PM
4	Prefer to not use the term "intermediate".	4/14/2015 1:56 PM
5	We do not agree with the term "intermediate," which our clinicians have told us they do not understand.	4/13/2015 2:11 PM
6	See previous comments on the use of "intermediate"	4/13/2015 1:13 PM
7	Like activity better because it also implies drug clearance rather than just enzyme function.	4/13/2015 10:22 AM
8	activity is better than function as no function remains to be elucidated	4/12/2015 8:36 AM
9	Opposed to "intermediate" because it doesn't imply directionality. Opposed to using "activity" to describe phenotypes AND alleles.	4/9/2015 3:34 PM
10	NO function is so absolute. see previous comments on this verbiage. Maybe no KNOWN function or no KNOWN activity.	4/9/2015 2:04 PM
11	Activity is more clear than function	4/9/2015 1:34 PM
12	I prefer to use the term "activity" rather than function as it may be possible that in the case of decreased gene expression, activity more accurately describes the phenotype than function and activity may also describe when an allele decreases a protein's functional capacity.	4/9/2015 12:35 PM
13	non-functional?	4/8/2015 11:12 AM
14	reduced better explains the functional state than intermediate	4/2/2015 7:26 AM
15	I do not favour the term intermediate	4/1/2015 12:45 PM
16	If high function alleles are discovered in the future, intermediate may be confused with normal, because something intermediate between no function and high function could be normal function.	4/1/2015 10:03 AM
17	Prefer Activity here	3/31/2015 1:37 PM
18	Clinically, the third list would be optimal when relaying results to patients.	3/27/2015 9:57 AM
19	Function being related to the gene/allele, whereas activity is related to the product (DME).	3/26/2015 10:17 PM
20	I'd argue against the use of the word "normal," as outlined in question 2.	3/26/2015 1:17 PM
21	prefer reduced to intermediate	3/26/2015 9:42 AM
22	prefer "reduced" rather than "intermediate" for function/activity	3/25/2015 10:29 PM
23	Reduced function/activity can be more easily confused with no function/activity.	3/25/2015 4:13 PM

Q7 Please indicate your acceptance to the set of terms below used to describe SLCO1B1 allele functional status. Note that SLCO1B1 is a transporter, not an enzyme. The percentage reported after each term indicates the percentage of experts from Delphi 1 who agreed or strongly agreed to that term. If you choose “not acceptable,” please explain why you do not think these terms are acceptable. You may also comment about acceptable terms:

Answered: 54 Skipped: 0



	Not Acceptable	Acceptable	Don't Know/No Opinion	Total	Weighted Average
Increased function (e.g. SLCO1B1*14) (80%); normal function (e.g. SLCO1B1*1) (91%); low function (e.g. SLCO1B1*5) (70%)	9.26% 5	87.04% 47	3.70% 2	54	1.90

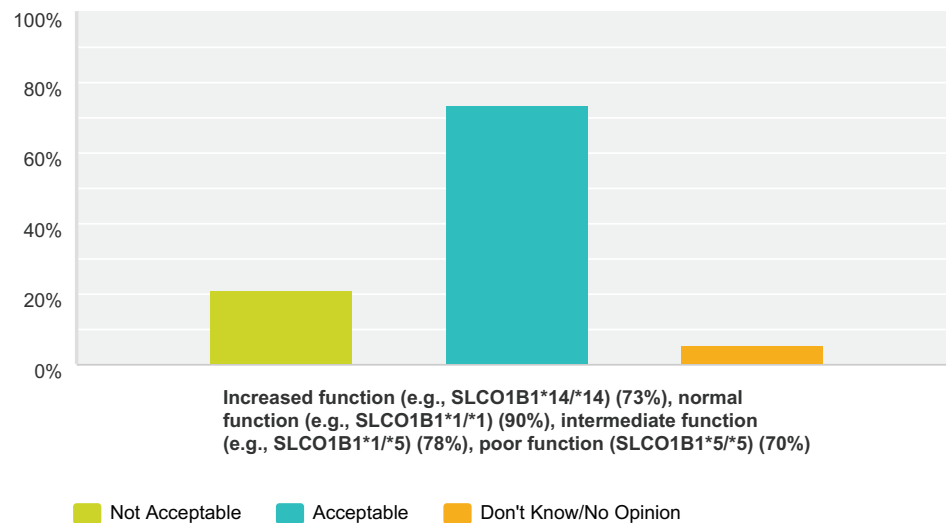
#	If you chose not acceptable, please explain which terms you think are not acceptable and why. You may also comment about acceptable terms:	Date
1	While "function" sounds more correct than "activity," especially because we're not talking about metabolic enzyme activity, it is still technically correct to state that a transporter has increased, normal or low activity (ability to perform its transporter function). To a clinician who doesn't think or care about these nuances, the concept will be the same. So I'd still use the same term (activity or function) that is chosen for the other alleles/phenotypes.	4/24/2015 4:29 PM
2	I think we should be consistent with our other selected terms. If we use "reduced" or "decreased" elsewhere, we should try to use the same term for SLCO1B1 (not "low"). Are the examples of alleles given to help the survey respondents or would they be included in the terms themselves? Previous questions placed examples below the comment box rather than in the term names. I do not support including examples of alleles in the names of terms.	4/17/2015 9:41 AM
3	Function in this case refers to transporter activity.	4/14/2015 2:27 PM
4	I'm surprised "decreased" or "reduced" function didn't make the cut for "low" function. Those would be more consistent with the CYP terms.	4/13/2015 1:18 PM

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5	Here, function is useful to represent this as a transporter. This may be a useful distinction for those who don't focus on pharmacodynamics. However, I prefer a 4-bin classification.	4/13/2015 10:27 AM
6	It is confusing to use the word "function" for either alleles or haplotypes across all PGx genes. Also, why use "low" when other genes use intermediate (which we oppose), decreased, or poor.	4/9/2015 3:51 PM
7	Was 'activity' deemed to be less appropriate than 'function' for transporters? Seems like the same conundrum should exist here too.	4/8/2015 11:14 AM
8	Decreased function instead of low function	4/8/2015 7:23 AM
9	I am not sure why transporters cannot have Activity? Transporter function or activity would be acceptable.	4/6/2015 1:10 PM
10	Why not "activity" as an alternative to "function" ?	4/1/2015 12:47 PM
11	Function for transporters appears reasonable. Activity for DME (not related to this question).	3/26/2015 10:19 PM
12	don't like "low function"; prefer "decreased function" to be like CYPs	3/26/2015 9:44 AM

Q8 Please indicate your acceptance for the set of terms below used to describe SLCO1B1 phenotype. Note that SLCO1B1 is a transporter, not an enzyme. The percentage reported after each term indicates the percentage of experts from Delphi 1 who agreed or strongly agreed to that term. If you choose “not acceptable,” please explain why you do not think these terms are acceptable. You may also comment about acceptable terms:

Answered: 53 Skipped: 1



	Not Acceptable	Acceptable	Don't Know/No Opinion	Total	Weighted Average
Increased function (e.g., SLCO1B1*14/*14) (73%), normal function (e.g., SLCO1B1*1/*1) (90%), intermediate function (e.g., SLCO1B1*1/*5) (78%), poor function (SLCO1B1*5/*5) (70%)	20.75% 11	73.58% 39	5.66% 3	53	1.78

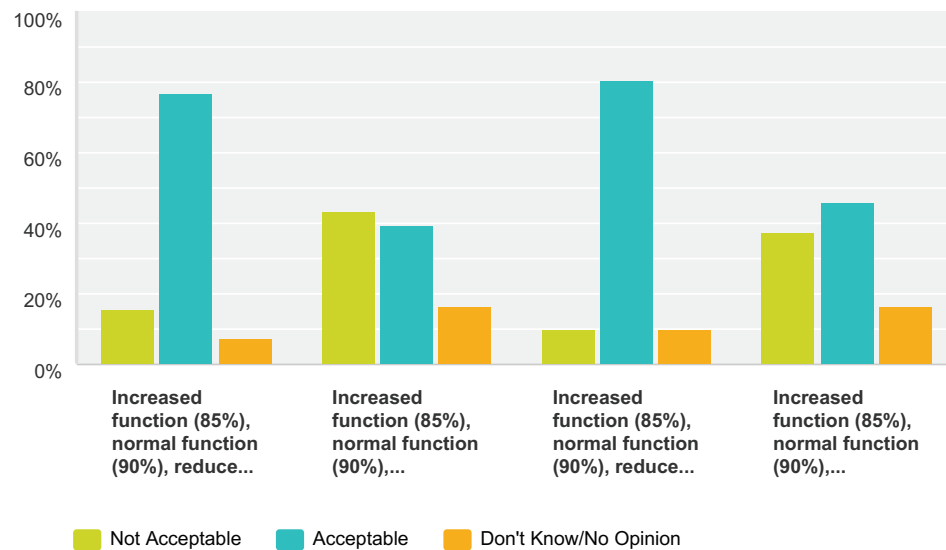
#	If you chose not acceptable, please explain which terms you think are not acceptable and why. You may also comment about acceptable terms:	Date
1	same comment about "function" vs. "activity" as for question 7	4/24/2015 4:29 PM
2	I selected "not acceptable" only because of the inconsistency in term selection for the lowest category. As stated previously, I think we should use "decreased function" rather than "poor function", which will be more consistent with other genes and pair better with "increased function". (If consensus is for "reduced" elsewhere, then that should be used here as well.)	4/17/2015 9:44 AM
3	Don't like "intermediate" (see other comments), what about "reduced"?	4/14/2015 2:45 PM
4	Prefer to not use term "intermediate".	4/14/2015 1:56 PM
5	We do not agree with the term "intermediate," which our clinicians have told us they do not understand.	4/13/2015 2:12 PM

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6	See my previous comments about the use of "intermediate". I think it should be "reduced" or "decreased". Perhaps in the cases where there is residual function with 2 decreased function alleles, we should use "very poor function"	4/13/2015 1:20 PM
7	Why not also add in to the mix the term non-functional?	4/10/2015 11:22 AM
8	Oppose using intermediate because it doesn't imply directionality - prefer "decreased". All other terms are acceptable.	4/9/2015 3:55 PM
9	Same issue with the term intermediate.	4/9/2015 3:40 PM
10		4/8/2015 11:18 AM
11	Per previous comments, should reduced function be considered?	4/2/2015 12:19 PM
12	I would prefer reduced or decreased function	4/2/2015 7:27 AM
13	There's no term for a *1/*14 patient. I don't like intermediate because when there's a high function and low function, intermediate and normal could be confused.	4/1/2015 10:08 AM
14	see previous comment	3/29/2015 2:37 PM
15	don't like intermediate - prefer decreased instead	3/26/2015 9:45 AM

Q9 Please indicate your acceptance to EACH set of terms below used to describe VKORC1 allele functional status. The percentage reported after each term indicates the percentage of experts from Delphi 1 who agreed or strongly agreed to that term (see table below for examples of possible alleles for the 4 different categories for each gene). If you choose “not acceptable,” please explain why you do not think these terms are acceptable. You may also comment about acceptable terms:

Answered: 53 Skipped: 1



	Not Acceptable	Acceptable	Don't Know/No Opinion	Total	Weighted Average
Increased function (85%), normal function (90%), reduced function (73%), no function (71%)	15.38% 8	76.92% 40	7.69% 4	52	1.83
Increased function (85%), normal function (90%), intermediate function (73%), no function (71%)	43.75% 21	39.58% 19	16.67% 8	48	1.48
Increased function (85%), normal function (90%), reduced function (73%), non-functional (78%)	9.80% 5	80.39% 41	9.80% 5	51	1.89
Increased function (85%), normal function (90%), intermediate function (73%), non-functional (78%)	37.50% 18	45.83% 22	16.67% 8	48	1.55

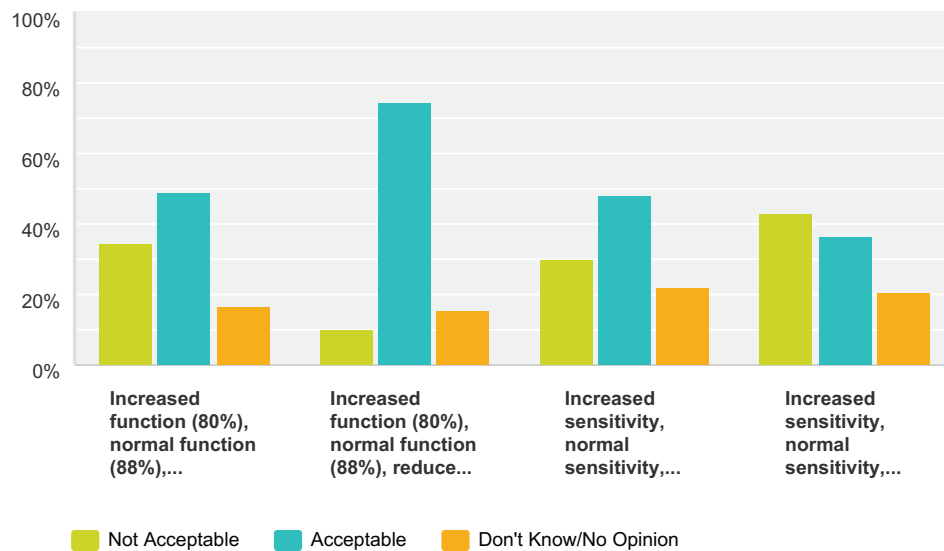
#	If you chose not acceptable, please explain which terms you think are not acceptable and why. You may also comment about acceptable terms:	Date
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1	Clinicians unfamiliar with the nuances may not understand that intermediate is less than normal. "non-functional" is inconsistent with the other terms ("function")	4/24/2015 4:31 PM
2	As stated previously, I think "intermediate" implies a category exists between itself and "none"; since the options that contain "intermediate" do not include a "decreased" option, I selected "not acceptable". Secondly, I'd prefer to see a "decreased" rather than "reduced" (since it pairs better with "increased").	4/17/2015 9:47 AM
3	See other comments re. use of "intermediate". I think that "no function" is a more consistent word choice than "non-functional", but don't feel this is a very important difference.	4/14/2015 2:46 PM
4	Vitamin K epoxide reductase complex subunit 1 is an enzyme that in humans is encoded by the VKORC1 gene. In the case of enzymes, I would prefer the use of the term "activity" (see previous comments).	4/14/2015 2:30 PM
5	Prefer to not use term "intermediate".	4/14/2015 1:56 PM
6	We do not agree with the term "intermediate," which our clinicians have told us they do not understand.	4/13/2015 2:12 PM
7	See my previous comments on the use of "intermediate"	4/13/2015 1:21 PM
8	I would just go with the consensus.	4/13/2015 10:30 AM
9	I prefer non-functional over no function	4/10/2015 11:23 AM
10	Oppose using "function" to describe allele status. Increased, normal, decreased, no modifiers are acceptable. Oppose using "intermediate" because it doesn't imply directionality. "decreased" is the opposite of "increased" not "reduced". The addition of "non-functional" adds complexity and inconsistency across the genes.	4/9/2015 3:59 PM
11	consider no KNOWN function instead of "no function or non-functional"	4/9/2015 2:06 PM
12	Although increased function variants are likely possible for VKORC1, I disagree strongly with using D36Y as an example of 'increased function'. To my knowledge, the mechanism behind warfarin resistance among D36Y carriers is not clear but has been suggested to be the result of structural interference with warfarin binding, not any change in enzyme activity or increased function.	4/9/2015 11:57 AM
13	'non-functional' and 'no function' can be used interchangeably. However, the 'non-functional' is an adjective, and 'no function' is a noun. Considering other terms are noun, the use of 'no function' should be preferred.	4/8/2015 12:41 PM
14	The use of the term Intermediate to describe allele function is confusing since it is often used to describe phenotype. Reduced Expression would also be acceptable.	4/6/2015 1:13 PM
15	Could intermediate be confusing when more than 2 categories of function are included?	4/2/2015 12:22 PM
16	prefer reduced over intermediate	4/2/2015 7:28 AM
17	I think intermediate and normal could be confused.	4/1/2015 11:00 AM
18	I'd argue against the use of "normal," as outlined in question 2.	3/26/2015 1:41 PM
19	prefer reduced to intermediate	3/26/2015 9:45 AM
20	prefer "non-functional" to "no-function"	3/25/2015 10:31 PM

Q10 Please indicate your acceptance of EACH set of terms below used to describe VKORC1 phenotype (see table below for examples of possible diplotypes for the 4 different categories). The percentage reported after each term indicates the percentage of experts from Delphi 1 who agreed or strongly agreed to that term. If you choose “not acceptable,” please explain why you do not think these terms are acceptable. You may also comment about acceptable terms:

Answered: 53 Skipped: 1



	Not Acceptable	Acceptable	Don't Know/No Opinion	Total	Weighted Average
Increased function (80%), normal function (88%), intermediate function (78%), no function (70%)	34.69% 17	48.98% 24	16.33% 8	49	1.59
Increased function (80%), normal function (88%), reduced function (70%), no function (70%)	9.80% 5	74.51% 38	15.69% 8	51	1.88
Increased sensitivity, normal sensitivity, reduced sensitivity, low sensitivity (terms added based on Delphi 1 results)	30.00% 15	48.00% 24	22.00% 11	50	1.62
Increased sensitivity, normal sensitivity, intermediate sensitivity, low sensitivity (terms added based on Delphi 1 results)	42.86% 21	36.73% 18	20.41% 10	49	1.46

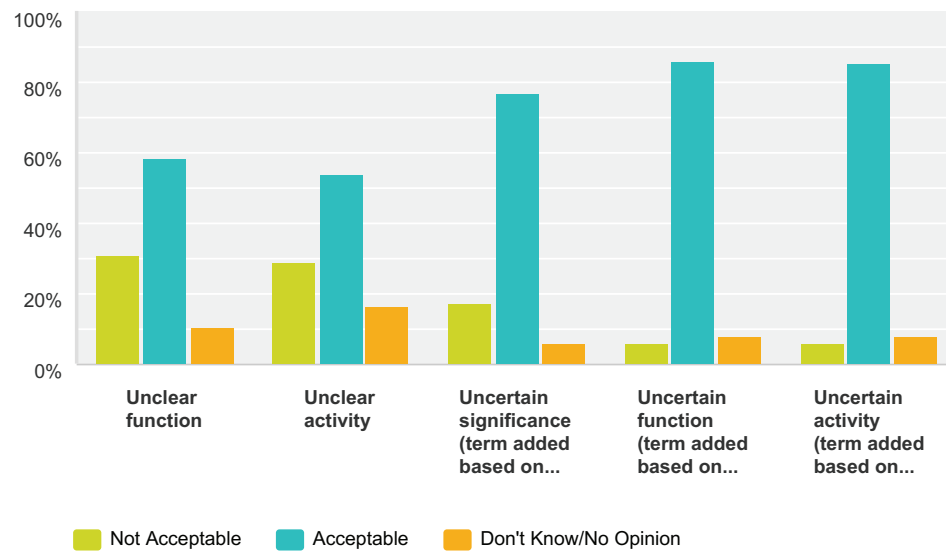
#	If you chose not acceptable, please explain which terms you think are not acceptable and why. You may also comment about acceptable terms:	Date
1	"Reduced" clearly indicates "less than normal" "Intermediate" is potentially ambiguous.	4/24/2015 4:33 PM

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2	Same comments as previous: 1) I do not prefer "intermediate" without "decreased", 2) I'd like to see "decreased" instead of "reduced". I do not like the term "sensitivity" since it is not specific. Increased sensitivity to what? A drug? An ADR? Which drug or ADR?	4/17/2015 9:50 AM
3	Refers to the clinical manifestation, i.e. warfarin sensitivity.	4/14/2015 2:31 PM
4	Prefer "reduced" to "intermediate". The use of "sensitivity" for VKORC1 exclusively is misleading, as CYP2C9 genotype also impacts dosing and patient sensitivity.	4/14/2015 2:29 PM
5	We do not agree with the term "intermediate," which our clinicians have told us they do not understand.	4/13/2015 2:12 PM
6	Sensitivity seems like it better described warfarin pharmacodynamics, not VKORC1 phenotype.	4/13/2015 1:45 PM
7	See my previous comments on the use of "intermediate"	4/13/2015 1:21 PM
8	I can live with any of these.	4/13/2015 10:32 AM
9	I think that the sensitivity term although commonly used can be misinterpreted by some clinicians.	4/10/2015 11:24 AM
10	What does "sensitivity" mean, relative to what? Increased function (80%), normal function (88%), reduced function (70%), no function (70%) - is OK, but prefer the word "decreased" instead of "reduced" since Increased and Decreased are antonym.	4/9/2015 4:01 PM
11	instead of NO function - consider no KNOWN function Intermediate is too vague. Keep it uniform across genes (increase/normal/reduced/no known activity)	4/9/2015 2:07 PM
12	As before, strongly disagree with including D36Y in the example of 'increased function'.	4/9/2015 11:58 AM
13	Sevsitivity is not a proper term altogether	4/8/2015 7:24 AM
14	Sensitivity to warfarin is dependent on VKORC1 and CYP2C9. Applying sensitivity to VKORC1 alone incorrectly minimizes the contribution of CYP2C9 genotypes.	4/6/2015 1:15 PM
15	In my opinion, the phenotype should describe the predicted protein function and not the sensitivity to a particular drug. As the field switches to panel testing/NGS the test name warfarin sensitivity will most likely not be reported in the EHR, but rather the EHR will contain a list of imporant pharmacogenes and associated diplotypes/phenotypes. Therefore, over time the term 'sensitivity' may have less meaning.	4/2/2015 12:33 PM
16	Prefer reduced over intermediate. Prefer function over sensitivity as this would introduce another term. Using the smallest number of terms across all genes would benefit a unified/standardized system	4/2/2015 7:32 AM
17	I think intermediate and normal could be confused.	4/1/2015 11:00 AM
18	Clinically sensitivity is easily misconstrude to mean 'allergy', 'adverse reaction', etc. It can also be misleading for patients to think they could be de-sensitized. The term functional is appropriate in the clinical setting because we're concerned about phenotypic presentation that a genotype relates.	3/27/2015 10:02 AM
19	A drug target. An individual may be more "sensitive" to the drug, not the drug target. Function for a dynamic target, not a DME.	3/26/2015 10:24 PM
20	I'd argue against the use of "normal," as outlined in question 2.	3/26/2015 1:42 PM
21	I find the term sensitivity confusing. I could live with intermediate, but refer reduced.	3/26/2015 9:47 AM
22	prefer "sensitivity" to "function" for VKORC1 variants and warfarin phenotype.	3/25/2015 10:33 PM
23	Description of function for VKORC1 adds an extra layer of complexity vs. simply stating effect on warfarin	3/25/2015 4:18 PM

Q11 Please indicate your acceptance of EACH term below used to describe allele function where the literature supporting the function is conflicting. If you choose “not acceptable,” please explain why you do not think these terms are acceptable. You may also comment about acceptable terms:

Answered: 53 Skipped: 1



	Not Acceptable	Acceptable	Don't Know/No Opinion	Total	Weighted Average
Unclear function	31.25% 15	58.33% 28	10.42% 5	48	1.65
Unclear activity	29.17% 14	54.17% 26	16.67% 8	48	1.65
Uncertain significance (term added based on Delphi 1 feedback and this is an ACMG term)	17.31% 9	76.92% 40	5.77% 3	52	1.82
Uncertain function (term added based on Delphi 1 feedback and this is an ACMG related term)	6.00% 3	86.00% 43	8.00% 4	50	1.93
Uncertain activity (term added based on Delphi 1 feedback and this is an ACMG related term)	6.12% 3	85.71% 42	8.16% 4	49	1.93

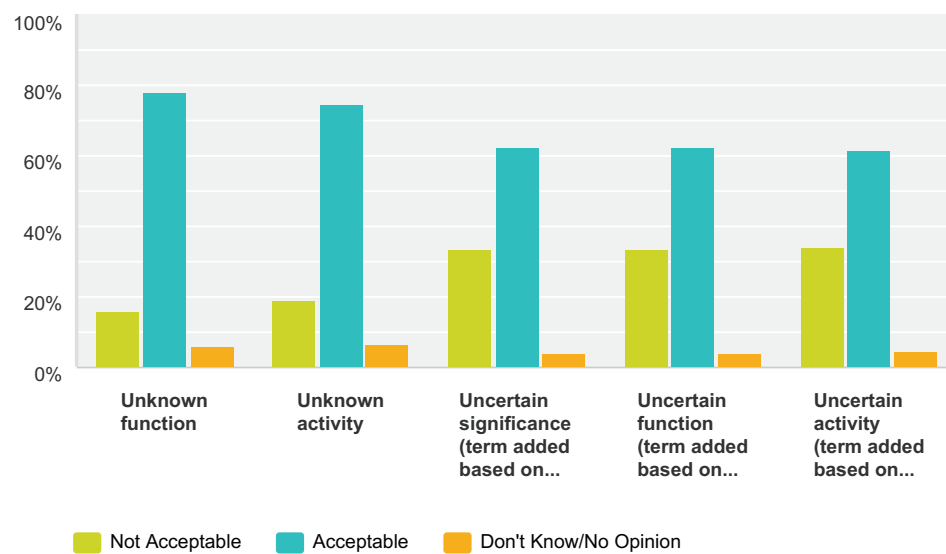
#	If you chose not acceptable, please explain which terms you think are not acceptable and why. You may also comment about acceptable terms:	Date
1	"Uncertain" is a more accurate and descriptive word than "unclear"	4/24/2015 4:35 PM
2	I do not like the use of "significance" to describe this level of evidence, which feels pre-clinical. If we do not yet understand the functional effect of a variant, we could call it unclear/uncertain. Because of that, we do not yet know how to apply it clinically. This could be different from a case where evidence shows a variant has a slight effect and is NOT conflicting, but due to the magnitude of the effect the change may have uncertain clinical significance. The terms "conflicting" and "significance" describe orthogonal concepts.	4/17/2015 10:04 AM
3	Prefer "uncertain" to "unclear".	4/14/2015 2:35 PM

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4	Function is a general "umbrella" term.	4/14/2015 2:33 PM
5	I don't really like the ACMG terms in this situtaiton.	4/13/2015 5:41 PM
6	I like staying with ACMG. Using the term significance allows us to apply it to all descriptive categories (function/activity/sensitivity)	4/13/2015 10:35 AM
7	"significance" is too vague. Prefer function to significance here.	4/12/2015 12:45 PM
8	Uncertain significance might be better just for us to stay consistent with the ACMG terms. However, ACMG refers to variants as have an uncertain significance not alleles. So Uncertain function or activity might be more appropriate in our context.	4/10/2015 11:27 AM
9	I think it is best to use ACMG related terms when possible.	4/10/2015 10:15 AM
10	"Function" should be reserved for diplotypes not alleles, or at the very least make sure that different terms are used to describe the status of alleles versus diplotypes.	4/9/2015 4:05 PM
11	unclear is too ... unclear (vague) :-)	4/9/2015 2:08 PM
12	I prefer the term "activity" over "function" when describing a variant's effects on a protein (unless it is clear that the function of the protein is affected).	4/9/2015 12:38 PM
13	My preference is to use the ACMG term '[variant of] uncertain significance' which is already accepted by physicians for hereditary genetic disease testing. All other terms listed are acceptable. It is better to have one term that indicates unclear or unknown function. There is no need to distinguish unclear function from unknown function.	4/6/2015 1:20 PM
14	Perfer uncertain	4/2/2015 12:39 PM
15	'significance' signalizes an interpretation of functional status. We should stick with terms describing function/activity. prefer uncertain over unclear	4/2/2015 7:38 AM
16	I would not favour the term sig nificance.	4/1/2015 12:53 PM
17	I prefer uncertain over unclear (just personal preference).	4/1/2015 11:02 AM
18	Unclear implies that results cannot be interpreted, not that results are conflicting. Significance is separate from function and pertains to whether a variant known to have differential function is clinically significant.	3/31/2015 1:44 PM
19	Would consider, "uncertain significance conflicting data" which separates it from the true "no data" cases	3/29/2015 2:40 PM
20	Function for gene/allele. Activity appears to relate to a DME.	3/26/2015 10:29 PM
21	"Unclear/uncertain function" makes it sound like we don't know exactly what the entire gene does, when taken out of context.	3/26/2015 1:57 PM
22	I think that VUS has been widely accepted in genetics, so prefer using uncertain over unclear	3/26/2015 9:50 AM
23	prefer "uncertain" for conflicting results	3/25/2015 10:35 PM

Q12 Please indicate your acceptance of EACH term below used to describe allele function where there is no literature describing function. If you choose “not acceptable,” please explain why you do not think these terms are acceptable. You may also comment about acceptable terms:

Answered: 53 Skipped: 1



	Not Acceptable	Acceptable	Don't Know/No Opinion	Total	Weighted Average
Unknown function	16.00% 8	78.00% 39	6.00% 3	50	1.83
Unknown activity	19.15% 9	74.47% 35	6.38% 3	47	1.80
Uncertain significance (term added based on Delphi 1 feedback and this is an ACMG term)	33.33% 16	62.50% 30	4.17% 2	48	1.65
Uncertain function (term added based on Delphi 1 feedback and this is an ACMG related term)	33.33% 16	62.50% 30	4.17% 2	48	1.65
Uncertain activity (term added based on Delphi 1 feedback and this is an ACMG related term)	34.04% 16	61.70% 29	4.26% 2	47	1.64

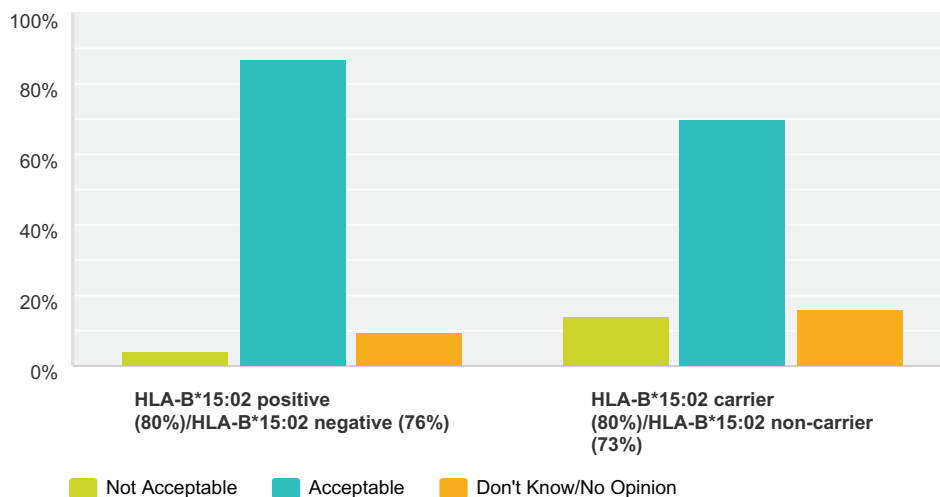
#	If you chose not acceptable, please explain which terms you think are not acceptable and why. You may also comment about acceptable terms:	Date
1	"Uncertain" implies conflicting data. "Unknown" implies missing data.	4/24/2015 4:35 PM
2	Overall, I prefer the more the more generalized term "function" over "activity". None of the terms that contain "uncertain" are acceptable because one cannot be "uncertain" without something to be "uncertain" about. Certainty requires an assertion or fact that can be evaluated and judged to be true or not true. If there is NO evidence, "unknown" is much better than "uncertain". If there is conflicting evidence or evidence of questionable quality, then "uncertain" would be appropriate (and "unknown" would be less so).	4/17/2015 10:04 AM
3	Prefer "unknown" if no literature exists to "uncertain".	4/14/2015 2:35 PM

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4	I don't really like the ACMG terms in this sitaiton.	4/13/2015 5:41 PM
5	Uncertain seems to describe conflicting events. If no literature description is available I prefer Unknown.	4/13/2015 4:27 PM
6	"uncertain" sounds to me that there is at least some literature available	4/13/2015 1:23 PM
7	Clearly implies no knowledge.	4/13/2015 10:35 AM
8	I think here "uncertain" is too vague---it's not uncertain, it's unknown!	4/12/2015 12:45 PM
9	Same comments as above.	4/10/2015 11:27 AM
10	We felt that uncertain encompassed both novel unknown and conflicting and therefore, although I don't have actual issues with the term unknown, its too much effort to have separate terms when in practice they lead to the same impact clinically.	4/9/2015 10:00 PM
11	Terms that are not acceptable are in conflict with ACMG guidance for "variants of uncertain significance". Under ACMG guidance there is no distinction between variants with conflicting versus no information. Rather, this is described in the variant details (sentences) of a clinical report.	4/9/2015 4:05 PM
12	I prefer the term "activity" over "function" when describing a variant's effects on a protein (unless it is clear that the function of the protein is affected).	4/9/2015 12:38 PM
13	There seem to be algorithms and bioinformatics resources available to ascertain possible consequences of a new or rare variant where there is not literature describing the effect. Thus it seems that we may be evolving where we 'know' something but are uncertain of the significance. In the bigger picture all might be OK but it may also be good to consider consistency with ACMG language.	4/8/2015 11:23 AM
14	My preference is to use the ACMG term '[variant of] uncertain significance' which is already accepted by physicians for hereditary genetic disease testing. All other terms listed are acceptable. It is better to have one term that indicates unclear or unknown function. There is no need to distinguish unclear function from unknown function.	4/6/2015 1:20 PM
15	Unknown may better capture that no literature/evidence is available. Uncertain may imply that data exists but the data is weak or conflicting.	4/2/2015 12:39 PM
16	if there is no literature, unknown much better describes the status quo than uncertain. Uncertain implies that some knowledge exists.	4/2/2015 7:38 AM
17	Uncertain is not appropriate if there are no data on the issue.	4/1/2015 12:53 PM
18	As above for significance. Uncertain would imply that there is literature describing function but difficult to interpret.	3/31/2015 1:44 PM
19	Function for gene/allele. Activity appears to relate to a DME.	3/26/2015 10:29 PM
20	"Unknown/uncertain function" makes it sound like we don't know exactly what the entire gene does, when taken out of context.	3/26/2015 1:57 PM
21	I think that VUS has been widely accepted in genetics, so prefer using uncertain over unclear	3/26/2015 9:50 AM
22	prefer "unknown" for no result.	3/25/2015 10:35 PM

Q13 Currently, there are 3 HLA-B alleles that are subject of CPIC guidelines and strongly associated with specific adverse effects to drugs (HLA-B*57:01 for abacavir hypersensitivity; HLA-B*58:01 for allopurinol cutaneous reactions, and HLA-B*15:02 for carbamazepine and phenytoin cutaneous reactions). Based on responses from Delphi 1, we are assuming that the PRESENCE and ABSENCE of each high risk allele should be documented. Please indicate your acceptance of EACH set of terms below used to describe HLA-B genotype. The percentage reported after each term indicates the percentage of experts from Delphi 1 who agreed or strongly agreed to that term. If you choose “not acceptable,” please explain why you do not think these terms are acceptable. You may also comment about acceptable terms:

Answered: 54 Skipped: 0



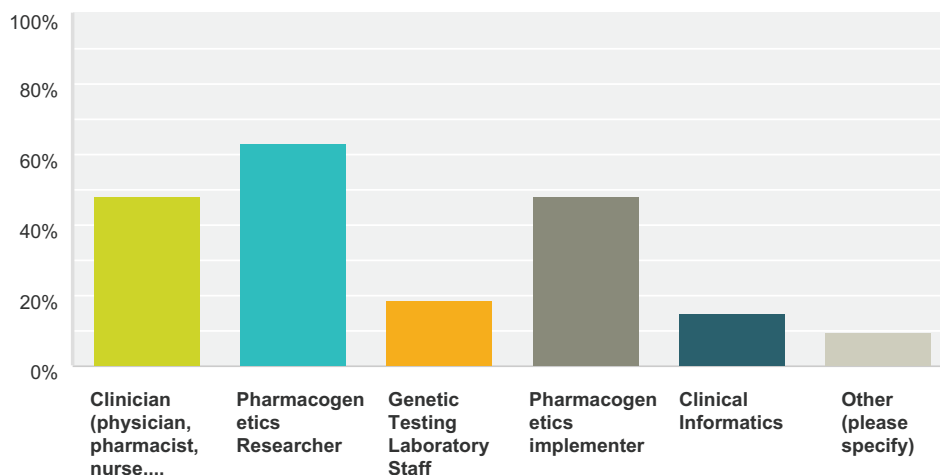
	Not Acceptable	Acceptable	Don't Know/No Opinion	Total	Weighted Average
HLA-B*15:02 positive (80%)/HLA-B*15:02 negative (76%)	3.77% 2	86.79% 46	9.43% 5	53	1.96
HLA-B*15:02 carrier (80%)/HLA-B*15:02 non-carrier (73%)	14.00% 7	70.00% 35	16.00% 8	50	1.83

CPIC Term Standardization for Clinical Pharmacogenetic Test Results: alleles and phenotypes-Delphi 2

#	If you chose not acceptable, please explain which terms you think are not acceptable and why. You may also comment about acceptable terms:	Date
1	The term "carrier" may be ok, but I wonder if its use in classical genetics would influence how the data is interpreted or used in the future. Secondly, I think it is important to note that when we designate HLA alleles using the "*x:y" nomenclature, we're specifying a PROTEIN sequence rather than a DNA sequence (allele).	4/17/2015 10:09 AM
2	I think that "positive" and "negative" is a more clear word choice than "carrier" vs "non-carrier" if the individual reading these terms isn't familiar with genetics terminology.	4/14/2015 2:49 PM
3	The term carrier is used in medical genetics to indicate whether a particular allele is present or not.	4/14/2015 2:36 PM
4	Either ok	4/13/2015 10:35 AM
5	lay people tend to associate negative with a bad outcome and could misinterpret this option	4/10/2015 11:28 AM
6	Since these variants act in a dominant manner, we should follow ACMG guidelines which is to report them as positive/negative rather than using carrier/non carrier. The purpose of a carrier test is different.	4/9/2015 4:06 PM
7	Positive/negative is a more clear yes or no.	4/9/2015 1:38 PM
8	Carrier is probably a more appropriate genetic term.	4/8/2015 11:23 AM
9	Carrier and non-carrier are genetics jargon.	4/6/2015 1:21 PM
10	prefer positive/negative as this is similar to how other genetic test results are reported in the oncology field.	4/2/2015 12:41 PM
11	carrier would also be acceptable, but I prefer positive/negative	4/2/2015 7:41 AM
12	Carrier status is well known to the lay public and to them refers to someone without the condition but the propensity to pass on to offspring. In this case, the presence of the allele is important for the individual tested.	3/29/2015 2:42 PM
13	traditionally in genetics the use of the term carrier has been confusing to physicians and patients. Voice of the customer feedback suggests that positive and negative are better to use. though does not whether patient is heterozygous or homozygous positive. Regardless of zygosity, if present, the drug is contraindicated.	3/26/2015 9:52 AM
14	prefer "carrier" over "positive"	3/25/2015 10:36 PM

Q14 What capacity are you involved in clinical pharmacogenetics (choose all that apply)?

Answered: 54 Skipped: 0

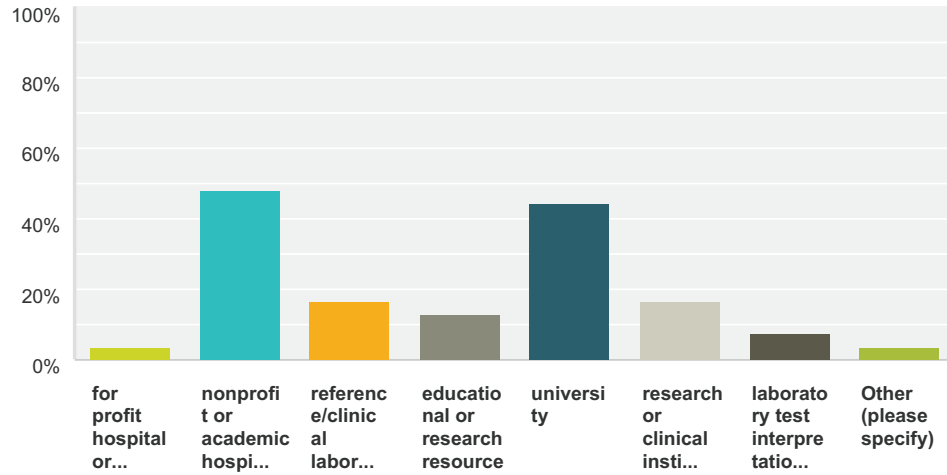


Answer Choices	Responses
Clinician (physician, pharmacist, nurse, etc.)	48.15% 26
Pharmacogenetics Researcher	62.96% 34
Genetic Testing Laboratory Staff	18.52% 10
Pharmacogenetics implementer	48.15% 26
Clinical Informatics	14.81% 8
Other (please specify)	9.26% 5
Total Respondents: 54	

#	Other (please specify)	Date
1	Lab Director	4/15/2015 11:41 AM
2	Genetic Counselor	4/13/2015 5:42 PM
3	Genetic Testing lab director	4/13/2015 4:28 PM
4	Scientific curator with PharmGKB	4/9/2015 12:39 PM
5	ontologist	4/8/2015 12:44 PM

Q15 Which of the following describes your workplace setting (choose all that apply)?

Answered: 54 Skipped: 0

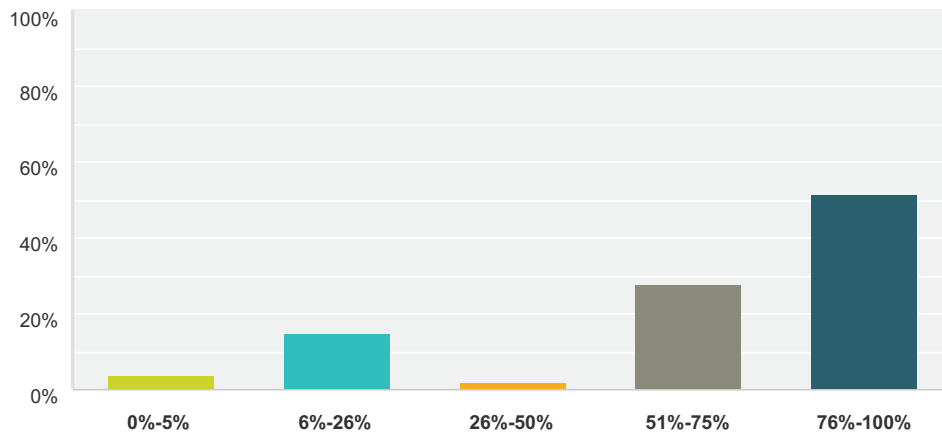


Answer Choices	Responses
for profit hospital or clinic	3.70% 2
nonprofit or academic hospital or clinic	48.15% 26
reference/clinical laboratory	16.67% 9
educational or research resource	12.96% 7
university	44.44% 24
research or clinical institute	16.67% 9
laboratory test interpretation service	7.41% 4
Other (please specify)	3.70% 2
Total Respondents: 54	

#	Other (please specify)	Date
1	Test developer and manufacturer	4/14/2015 10:23 PM
2	Knowledgebase	4/9/2015 12:39 PM

Q16 What percentage of time do you devote to pharmacogenetics (i.e. research time, clinic time, etc.)?

Answered: 54 Skipped: 0



Answer Choices	Responses	
0%-5%	3.70%	2
6%-26%	14.81%	8
26%-50%	1.85%	1
51%-75%	27.78%	15
76%-100%	51.85%	28
Total		54