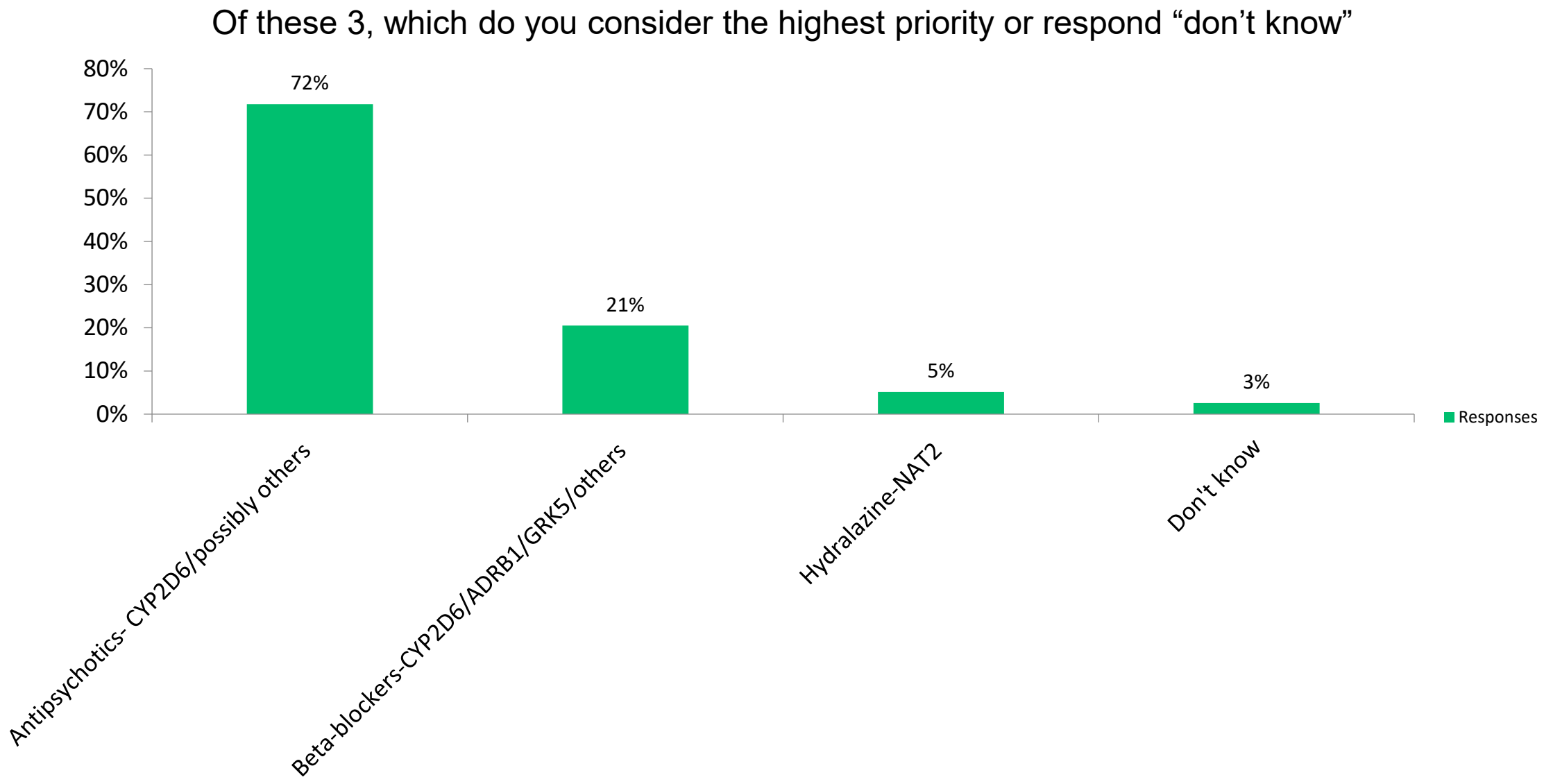
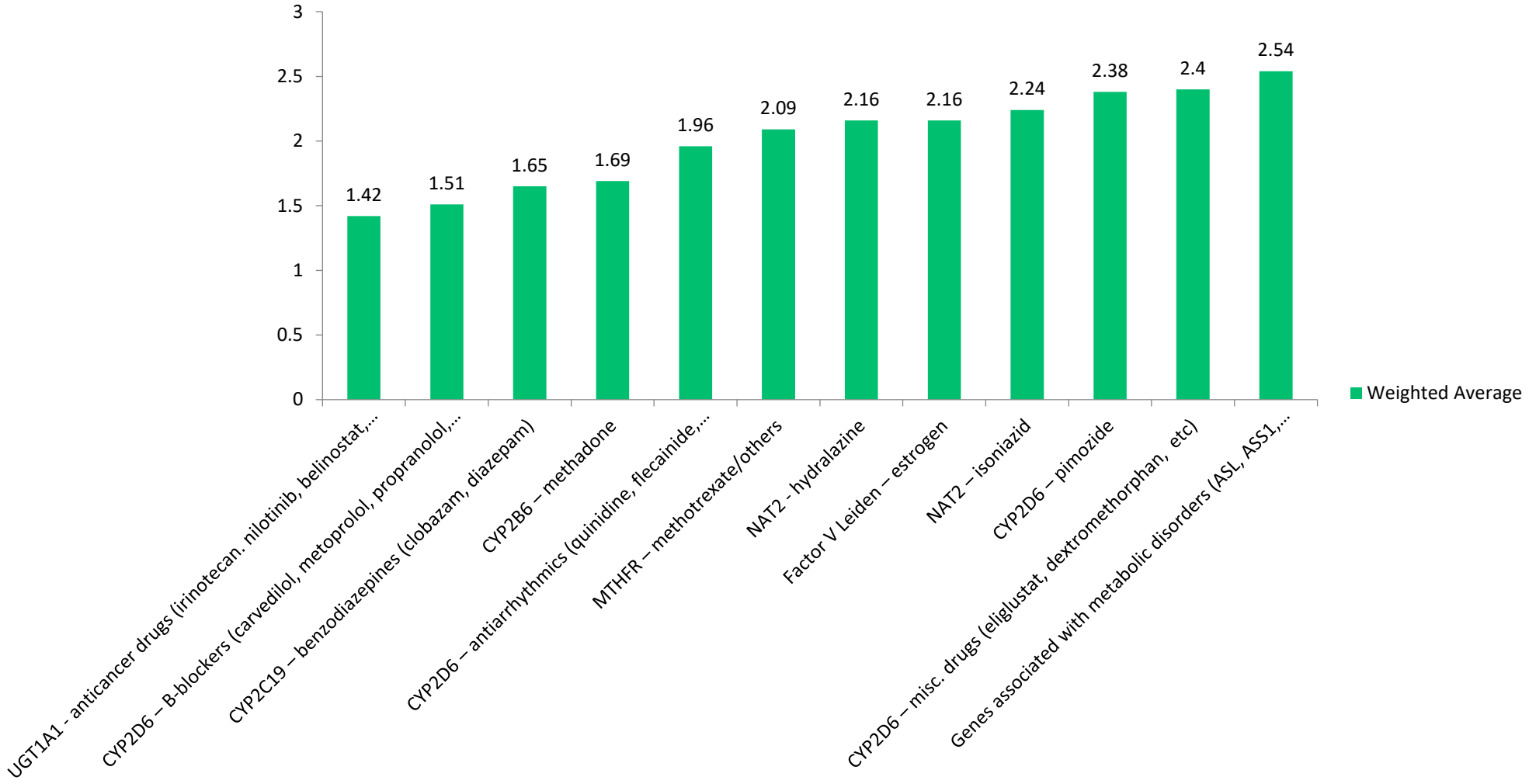
Member survey for guideline prioritization

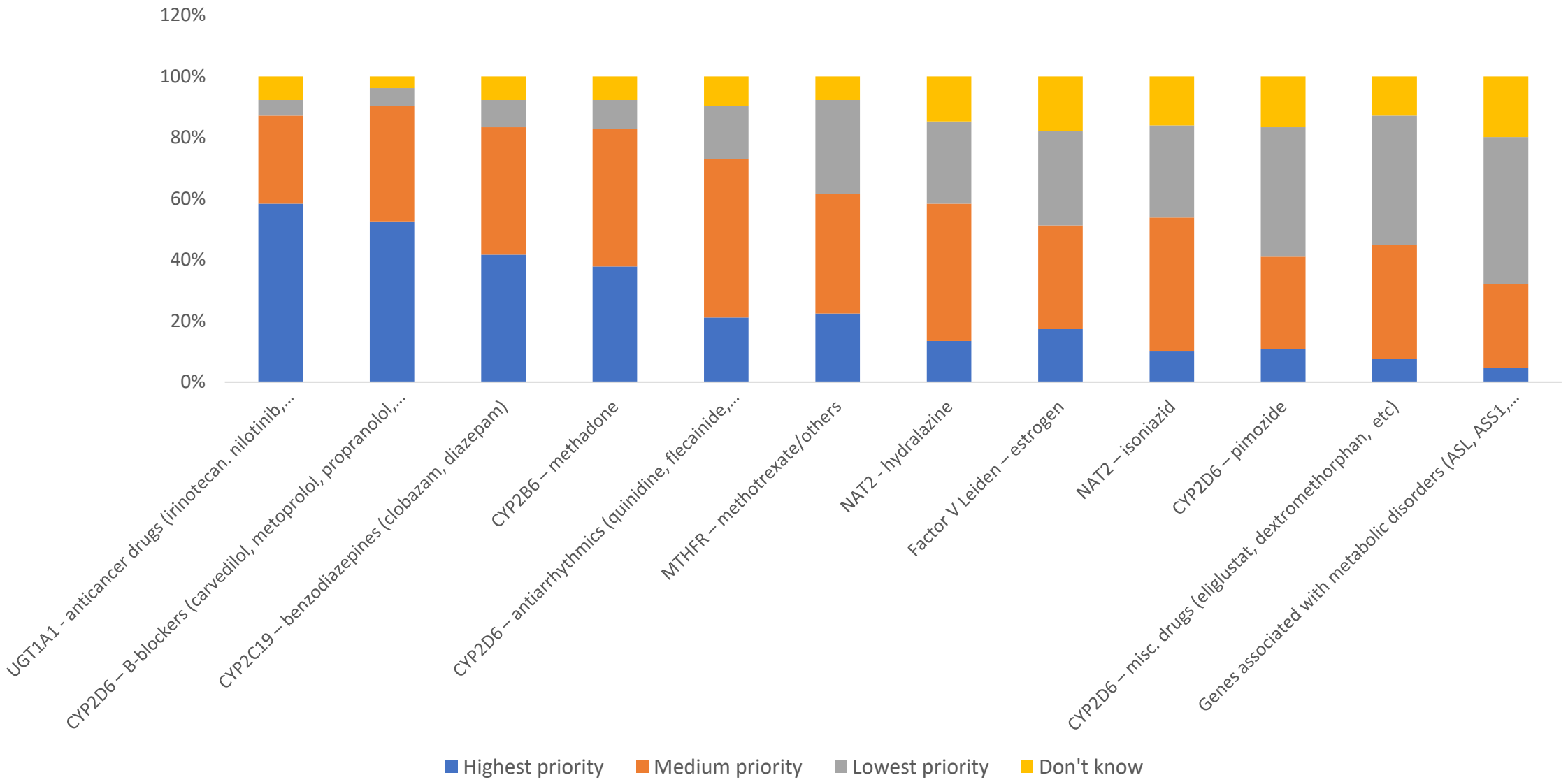

Of these 3, which do you consider the highest priority or respond “don’t know”
80%
70%
60%
50%
40%
30%
20%
10%
0%
72%
21%
5%
3%
Responses
Antipsychotics- CYP2D6/possibly others
Beta-blockers-CYP2D6/ADRB1/GRK5/others
Hydralazine-NAT2
Don’t know

n=156

Rank the following gene/drug groups for their priority as the subject of a new CPIC guideline (highest priority, medium priority, lowest priority,



n=156


120%
100%
80%
60%
40%
20%
0%
UGT1A1 - anticancer drugs (irinotecan, nilotinib,...
CYP2D6 – B-blockers (carvedilol, metoprolol, propranolol,...
CYP2C19 – benzodiazepines (clobazam, diazepam)
CYP2B6 – methadone
CYP2D6 – antiarrhythmics (quinidine, flecainide,...
MTHFR – methotrexate/others
NAT2 - hydralazine
Factor V Leiden – estrogen
NAT2 – isoniazid
CYP2D6 – pimozide
CYP2D6 – misc. drugs (eliglustat, dextromethorphan, etc)
Genes associated with metabolic disorders (ASL, ASS1,...
Highest priority
Medium priority
Lowest priority
Don't know

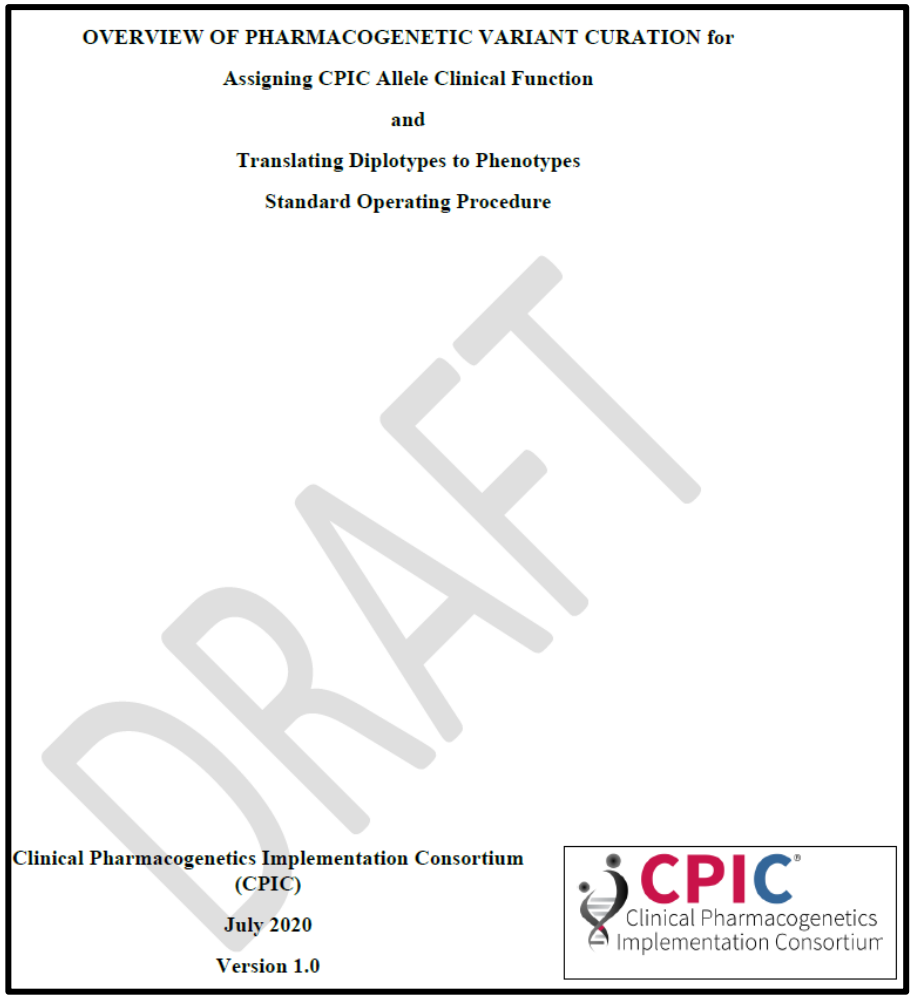
Guideline prioritization

Antipsychotics- CYP2D6/possibly others
CYP2D6 – B-blockers (carvedilol, metoprolol, propranolol, timolol)
UGT1A1 - anticancer drugs (irinotecan. nilotinib, belinostat, others)
CYP2C19 – benzodiazepines (clobazam, diazepam)
CYP2B6 – methadone
CYP2D6 – antiarrhythmics (quinidine, flecainide, propafenone)
MTHFR – methotrexate/others
NAT2 - hydralazine
Factor V Leiden – estrogen
NAT2 – isoniazid
CYP2D6 – pimozide
CYP2D6 – misc. drugs (eliglustat, dextromethorphan, etc)
Genes associated with metabolic disorders (ASL, ASS1, CPS1, NAGS, OTC, GBA, HPRT1, NAGS, POLG, etc) – various drugs (valproic acid, velagluceras alfa, mycophenolic acid, carglumic acid, etc)

Updated allele function SOP

Pharmacogene Curation SOP

- Describes procedures for
  - expert selection and training
  - evidence collection and inclusion of alleles
  - assigning strength of evidence and allele function
  - summarizing the evidence
  - translating diplotypes to phenotypes
  - re-evaluations and updates



Professional Training

- Required for all experts

Conference Call

- Review Pharmacogene Curation SOP
- Record call

Assessment

- Purpose: assess expert's understanding of SOP
- Example of 10 question assessment
- Disseminated with recording of the conference call
- Must be completed prior to next scheduled conference call

Coaching

- Required if scored <80% on the assessment and must retake assessment
- By request or at the discretion of the CPIC facilitator

CPIC Assessment of Expert Understanding of Pharmacogene Curation SOP

Author Expert: _____ Date: _____

Please mark the correct answers and submit.

1. Evidence used to assign allele clinical function include:
   a. Clinical studies
   b. In vitro experimental data
   c. Unpublished data
   d. A & B

2. Sections of the allele functionality table which must be completed for every allele include:
   a. Allele clinical functional status
   b. Summary of Findings
   c. Strength of evidence
   d. All of the above

Scoring the Evidence Process Overview

- Two authors will independently
  - assign strength of evidence
  - assign allele clinical function
  - assign activity value for genes using activity scores
  - summarize the evidence
- Independent evaluations are compiled into a working draft of the Allele functionality table
- Table is disseminated to all other authors for review

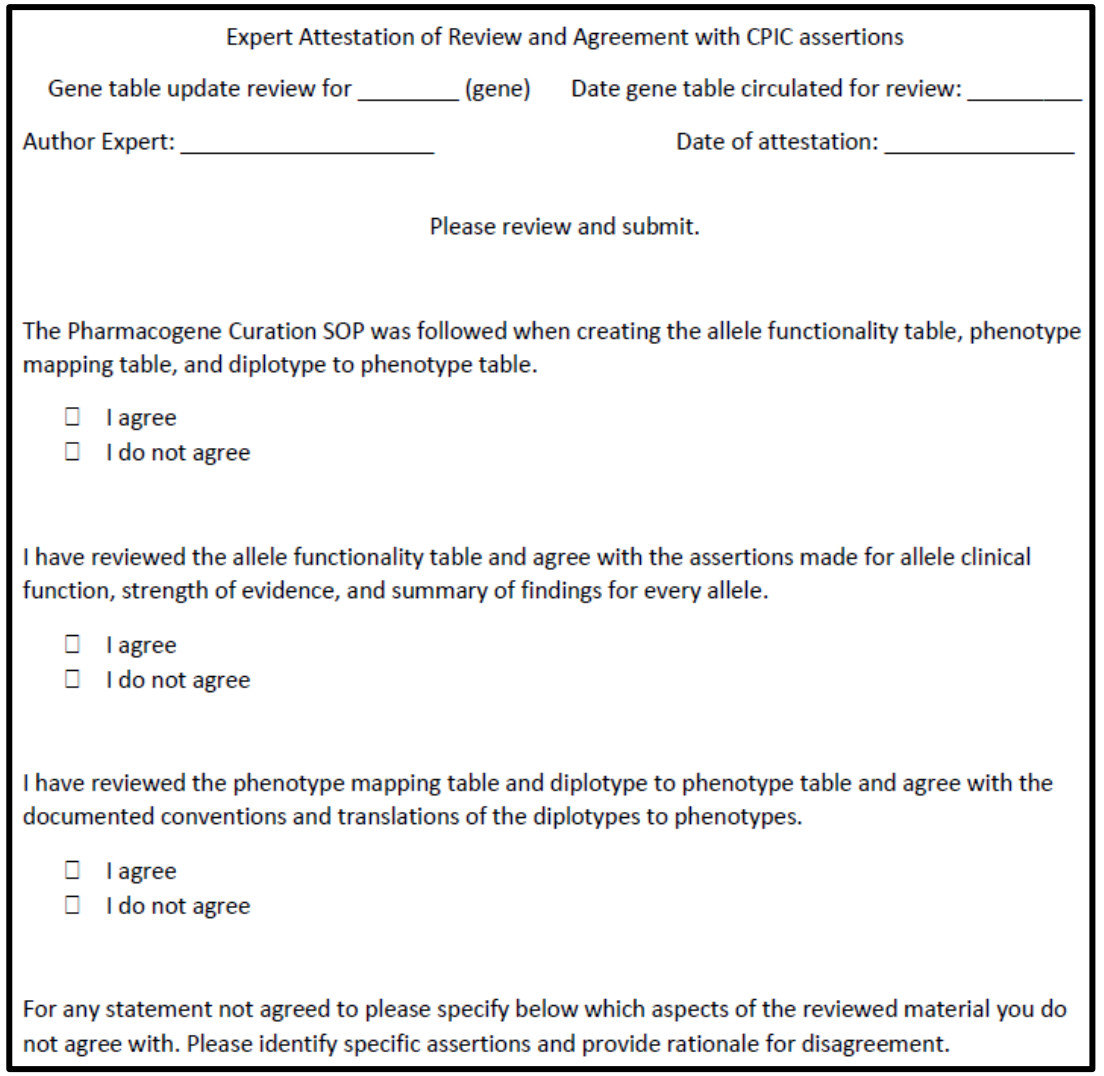
Allele/cDNA/rsID	Activity Value (Optional)	Allele Biochemical Functional Status (Optional)	Allele Clinical Functional Status (Required)	Allele Clinical Function Substrate Specificity (Optional)	PMID (Required)	Strength of Evidence (Required)	Summary of Findings (Required)
*1	1	Normal Function	Normal Function				
*2	0.5	Decreased function	Decreased function		29283396; 20150829; 15637526; 12742136; 10413320; 27179628; 25775139; 19082874;	Definitive	CYP2C9*2 is assigned decreased function based on definitive evidence in homozygous and heterozygous patients and in vitro experimental data. CYP2C9*2 has been studied for more than 20 years and its association with impaired function compared to wildtype is well-established (29283396, 20150829, 15637526). The phenotype for patients homozygous for the CYP2C9*2 variant was updated from poor metabolizer to intermediate metabolizer after reevaluation of prior and new evidence demonstrating CYP2C9*2 has more enzyme activity than CYP2C9*3, which results in in a similar phenotype for

Evidence Summary

- (a) summarizes the evidence supporting the assigned allele function
  - must note if it is a well-established association that did not require a primary literature review
  - may point to an authoritative resource for allele function
- (b) notes conflicting evidence and summarizes the experts' assessment of this evidence
  - includes consensus and rationale for final assertion if there was disagreement among experts
- (c) notes if an assertion was modified based on clinical expertise
  - includes the original assertion and the experts' rationale for modification

Expert Attestation

- Attestation of expert review and agreement with the assertions in the evidence table is required
- Documents consensus achieved among at least 70% of experts
- Ensures evidence summaries adequately capture consensus, rationale, and acknowledgment of disagreements



Expert Attestation of Review and Agreement with CPIC assertions

Gene table update review for _____ (gene) Date gene table circulated for review: _____

Author Expert: _____ Date of attestation: _____

Please review and submit.

The Pharmacogene Curation SOP was followed when creating the allele functionality table, phenotype mapping table, and diplotype to phenotype table.

- ☐ I agree
- ☐ I do not agree

I have reviewed the allele functionality table and agree with the assertions made for allele clinical function, strength of evidence, and summary of findings for every allele.

- ☐ I agree
- ☐ I do not agree

I have reviewed the phenotype mapping table and diplotype to phenotype table and agree with the documented conventions and translations of the diplotypes to phenotypes.

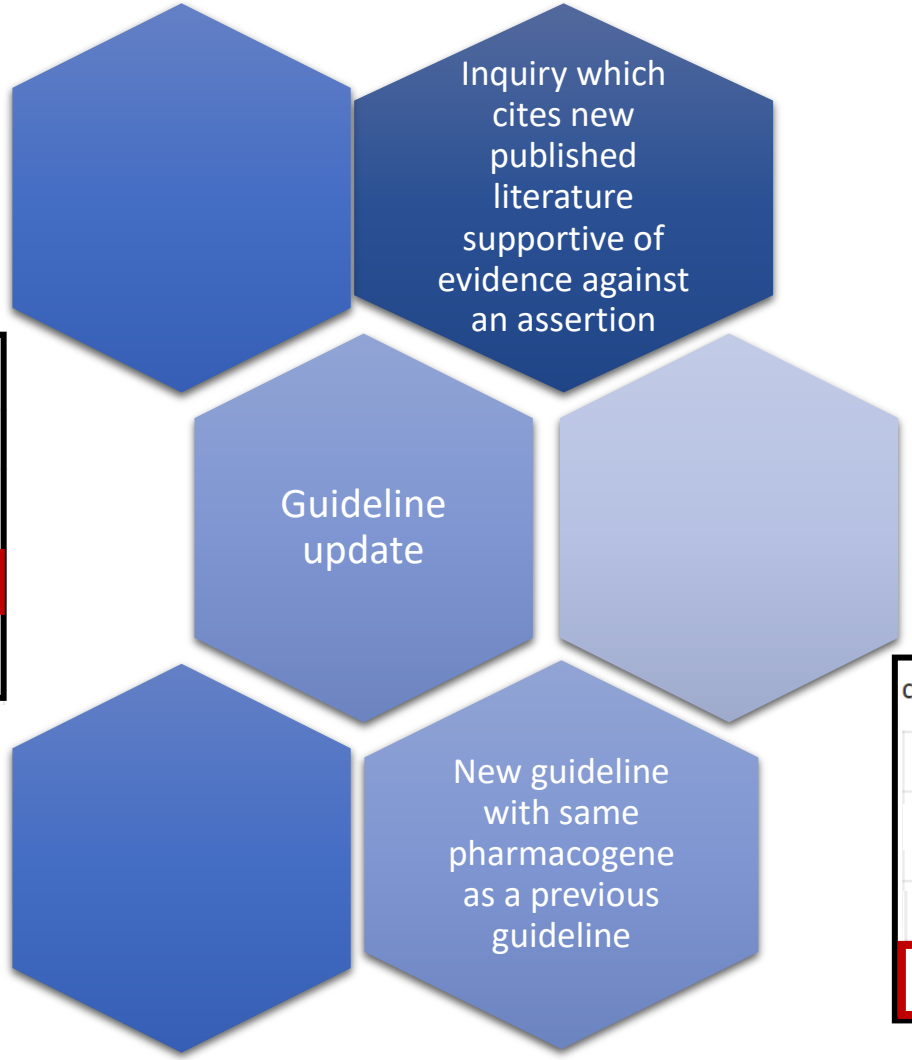
- ☐ I agree
- ☐ I do not agree

For any statement not agreed to please specify below which aspects of the reviewed material you do not agree with. Please identify specific assertions and provide rationale for disagreement.

Three ways to initiate re-evaluations and updates

CPIC guidelines published, in progress, or planned

Gene – Drug	Status
CYP2D6, CYP2C19 – TCAs	Published
SLCO1B1 – simvastatin	Published; **update in progress**
CYP2C19, CYP2D6 – antidepressants (SNRI/NaSSA)	**In progress**



CPIC guidelines published, in progress, or planned

Gene – Drug	Status
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SLCO1B1 – simvastatin	Published; **update in progress**
CYP2C19, CYP2D6 – antidepressants (SNRI/NaSSA)	**In progress**

https://cpicpgx.org/prioritization-of-cpic-guidelines/

Genes with updated tables

- CYP2C9
  - Sent to CYP2C9 authors for review
  - Authors need to take the assessment and attestation
- CYP2C19
  - Authors of current CYP2C19 guidelines (clopidogrel and SSRI) will go through process of re-evaluations
  - Once final, will send to other CYP2C19 guideline authors (e.g., voriconazole, TCAs, PPIs, etc) for approval
  - All authors need to take the assessment and attestation
- CYP2D6-underway
- SLCO1B1-guideline being updated now

Process for re-evaluations due to updated guideline or guideline with same pharmacogene as a previous guideline