Prioritization of Genes and Drugs for CPIC Guideline Development

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CPIC genes and drugs

# (N=199)	GENE (UNIQUE = 65)	DRUG (UNIQUE = 155)	GUIDELINE ON PHARMGKB	CPIC LEVEL	PHARMGKB LEVEL OF EVIDENCE	PGX ON FDA LABEL	CPIC PUBLICATIONS (PMID)
1	HLA-B	abacavir	Guideline	A	1A	Genetic testing recommended	CPIC abacavir guideline • 22378157 • 24561393
2	HLA-B	allopurinol	Guideline	A	1A		CPIC allopurinol guideline • 23232549
3	CYP2C19	amitriptyline	Guideline	A	1A		CPIC TCAs guideline • 23486447

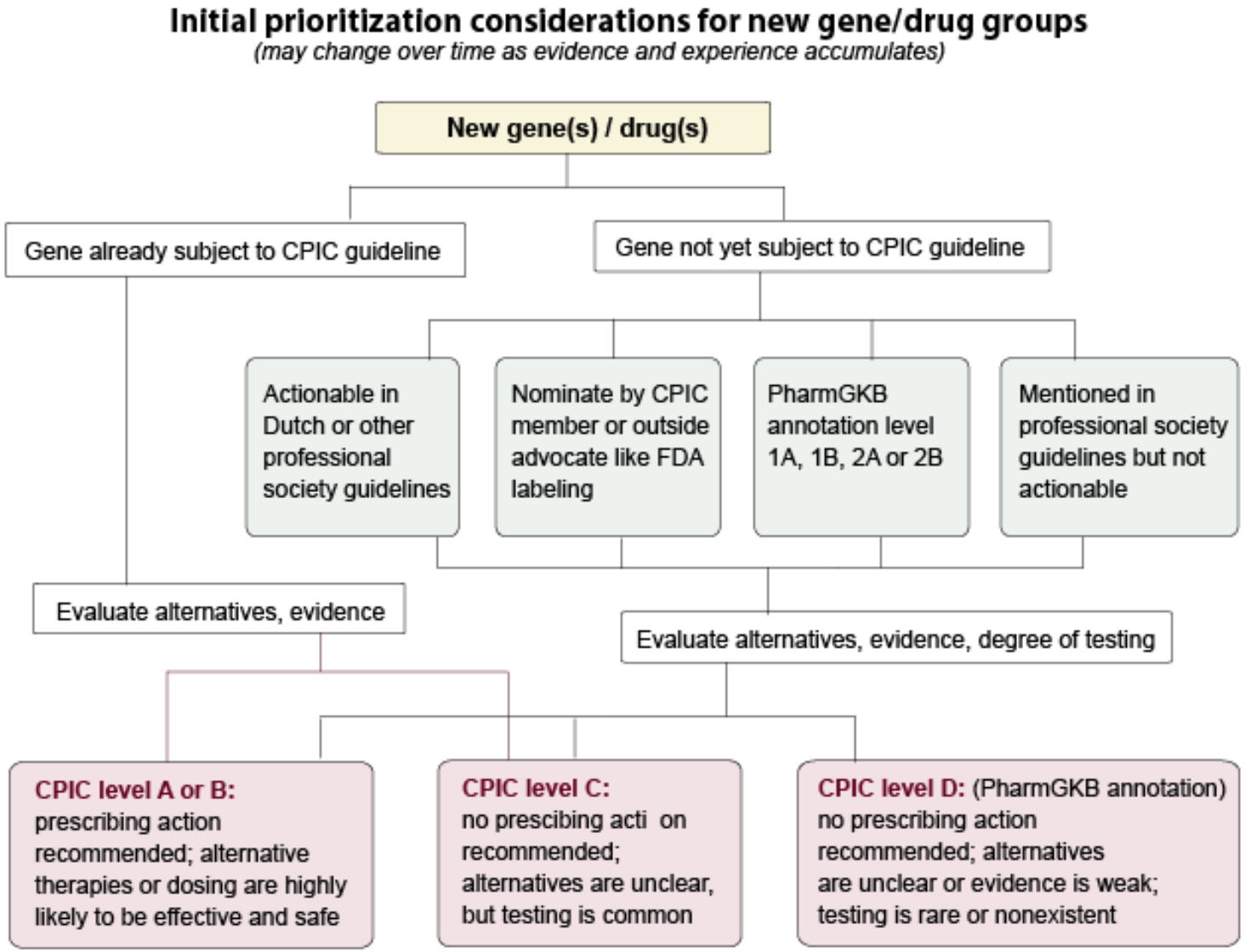
https://cpicpgx.org/genes-drugs/

CPIC level definitions

CPIC LEVEL	CLINICAL CONTEXT	LEVEL OF EVIDENCE	STRENGTH OF RECOMMENDATION
A	Genetic information should be used to change prescribing of affected drug	Preponderance of evidence is high or moderate in favor of changing prescribing	At least one moderate or strong action (change in prescribing) recommended.
B	Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing	Preponderance of evidence is weak with little conflicting data	At least one optional action (change in prescribing) is recommended.
C	There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics makes no convincing difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical or (c) few published studies or mostly weak evidence and clinical actions are unclear. Most important for genes that are subject of other CPIC guidelines or genes that are commonly included in clinical or DTC tests.	Evidence levels can vary	No prescribing actions are recommended.
D	There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. If the genes are not widely tested for clinically, evaluations are not needed.	Evidence levels can vary	No prescribing actions are recommended.

https://cpicpgx.org/prioritization/#cpicLevels

Algorithm for CPIC gene/drug prioritization



https://cpicpgx.org/prioritization/#flowchart

1. New gene/drug brought up for consideration

For example,

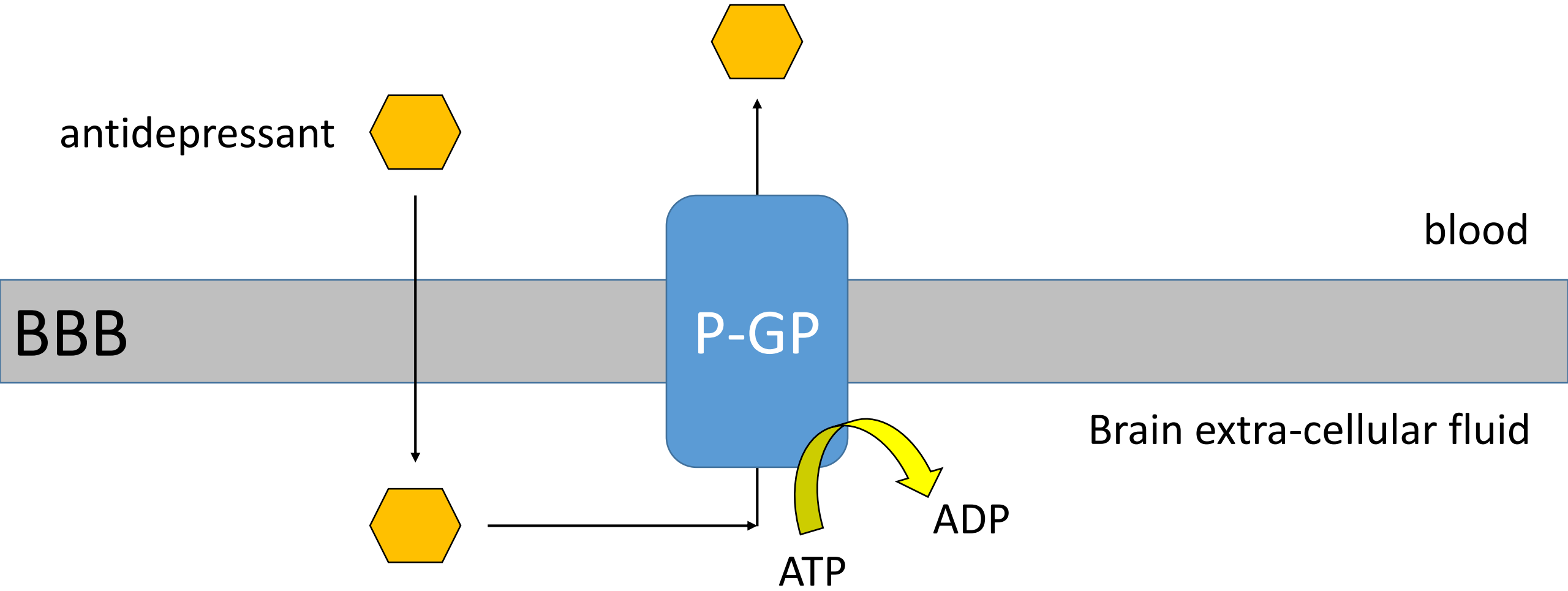
ABCB1/antidepressants

Is this gene the subject of a current CPIC guideline?

No

1. New gene/drug brought up for consideration

ABCB1/antidepressants



2. Have other groups already explored this gene?

	ABCB1/antidepressants
Actionable in Dutch or other professional society guidelines?	No
Nominated by CPIC member or outside advocate like FDA labeling?	Yes - CPIC member
What is the PharmGKB annotation level?	Level 3 (low evidence)
Mentioned in professional society guidelines but not actionable?	No

3. Evaluate alternatives

ABCB1/antidepressants

- Selective Serotonin Reuptake Inhibitors (SSRIs)
  - Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
- Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)
  - Duloxetine, desvenlafaxine, venlafaxine
- Tricyclic Antidepressants (TCAs)
  - Amitriptyline, clomipramine, nortriptyline, imipramine
- Other agents
  - Buproprion, mirtazapine, trazodone

4. Evaluate the evidence

PubMed Keywords:

(ABCB1 or MDR1) and antidepressants

29 original articles, 3 meta-analyses

4. Evaluate the evidence

	A	B	C	D	E	F	G	H	I	J
1	Study	Year	PMID	Study Design	Description	Sample Size	rs2032583	rs2235015	rs2235040	rs1045642
2	Schatzberg, et al	2015	25815420	Clinical Trial	Examined *ABCB1* ger	n = 683	X	X		
3	Bet, et al	2015	25987242	Cohort	Investigated the ass	n = 789				
4	Chang, et al	2015	26598582	Cohort	Investigated possibl	n = 112				X
5	Jelen, et al	2015	26664259	Cohort	The objective of this	90 genotyped; 96 controls				X
6	Breitenstein, et al	2015	26704739	Clinical Trial	The aim of the curre	73 genotyped; 128 controls	X	X		
7	Breitenstein, et al	2014	23880209	Cohort	The aim of the prese	58 genotyped; 58 controls	X	X		
8	Ozbey, et al	2014	24911075	Cohort	The current study air	n = 54				X
9	de Klerk, et al	2013	22641028	Cohort	Conducted a study ir	n = 424	X	X	X	X
10	Karlsson, et al	2013	23515680	Cohort	In this study, we ain	n = 228				X
11	Noordam, et al	2013	23771194	Cohort	The objective of this	n = 1257				X
12	Boiso Moreno, et al	2013	23820292	Cohort	The aim of this study	n = 998				X
13	Huang, et al	2013	24192121	Cohort	Investigated whethe	n = 290				
14	Singh, et al	2012	23188198	Cohort	The aims of this stuc	n = 98				X
15	Lin, et al	2011	20859246	Cohort	Tested whether gene	n = 100				X
16	Perlis, et al	2010	20110084	Clinical Trial	This analysis examir	n = 250	X		X	
17	Rosenhagen, et al	2010	20520302	Case Report	The aim of these cas	n = 2				
18	Sarginson, et al	2010	20555295	Clinical Trial	Sought to determine	n = 246	X	X	X	X
19	Menu, et al	2010	20664232	Cohort	The objective of this	n = 117				X
20	Dong, et al	2009	19844206	Cohort	Studied seven genes	n = 142				
21	Kato, et al	2008	17913323	Cohort	Examined the possib	n = 68				X
22	Uhr, et al	2008	18215618	Cohort	Analyzed the associa	n = 443	X	X	X	
23	Peters, et al	2008	18382661	Case-control	Sought to determine	n = 1953				X
24	Mihaljevic Peles, et al	2008	18550244	Cohort	Aims of the study we	n = 127				X
25	Gex-Fabry, et al	2008	18641553	Cohort	Investigated plasma	n = 71				X
26	Nikisch, et al	2008	18940259	Cohort	Examined the influe	n = 15				X

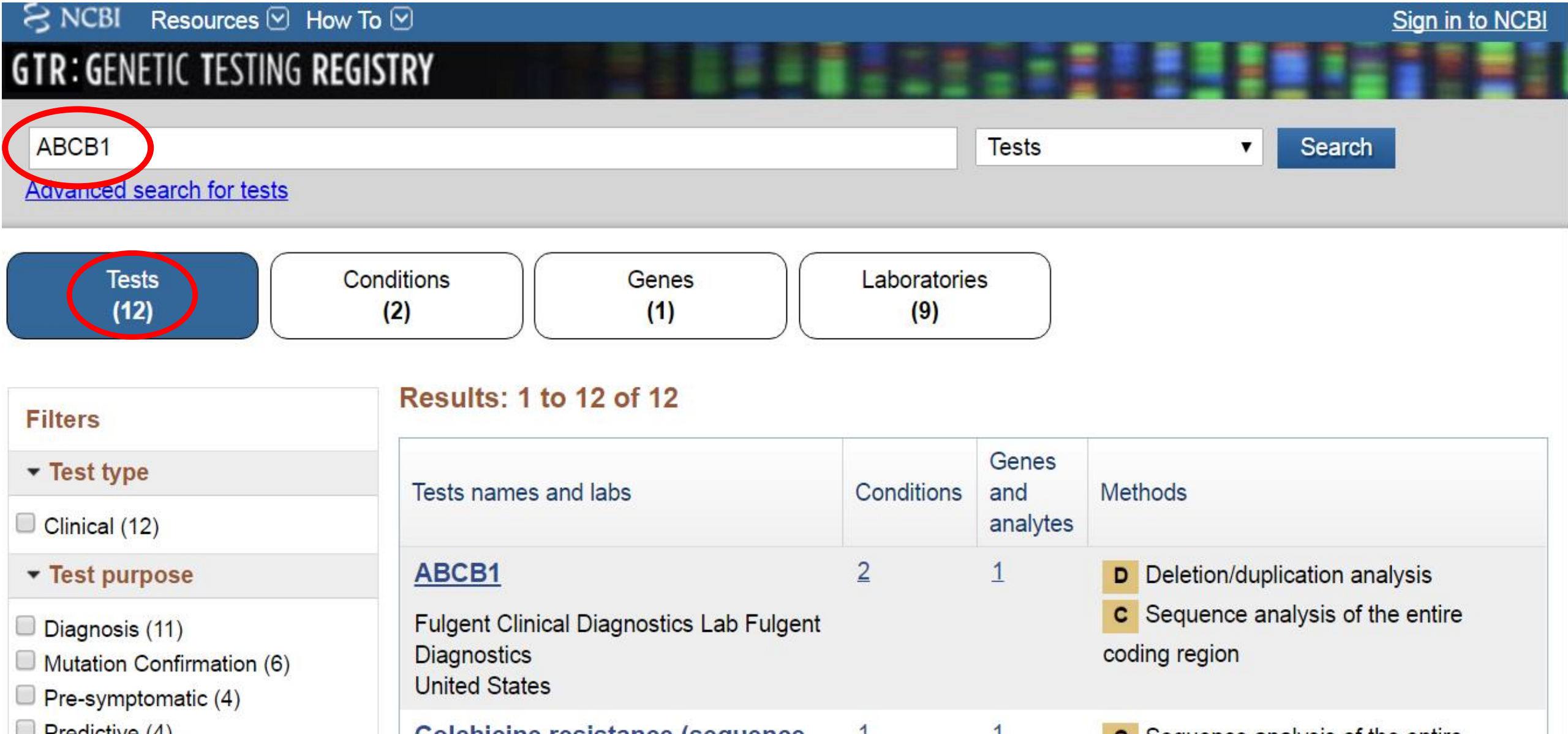
Primary Literature | Meta-Analyses | ABCB1 SNPs

4. Evaluate the evidence

ABCB1 SNP	Association Found	No Association Found
rs2032583	5	2
rs2235015	3	3
rs2235040	3	1
rs1045642	9	10
rs1128503	3	6
rs2032582	4	9

Need further analysis: study quality, antidepressants included, clinical endpoints – efficacy vs. safety, etc.

5. Evaluate the degree of testing



6. Assign CPIC level to gene/drug pair

Actionable

At least one change in prescribing is recommended

Not Actionable

No prescribing actions are recommended

CPIC levels A and B are *actionable*

Genetic information **should** be used to change prescribing of affected drug.

Genetic information **could** be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing.

CPIC levels C and D are *not actionable*

C

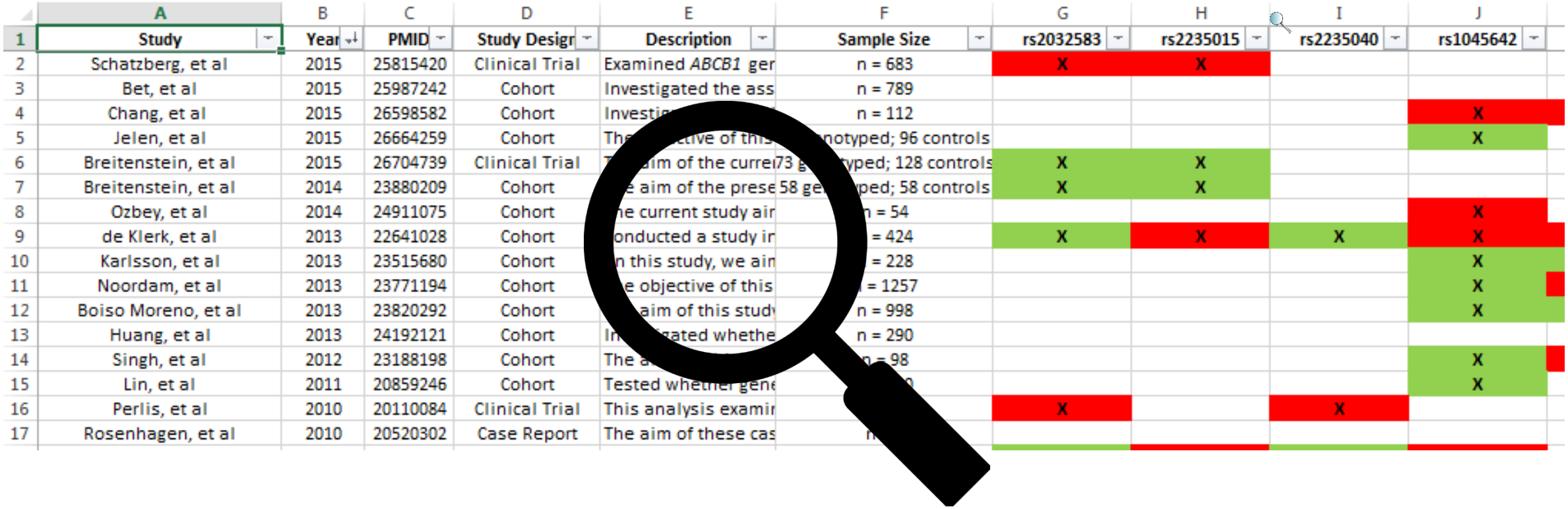
There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics makes no convincing difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical or (c) few published studies or mostly weak evidence and clinical actions are unclear. Clinical testing is common.

D

There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. Clinical testing is rare.

Next steps for *ABCB1*/antidepressants

- Needs further investigation
  - Closer look at evidence by experts



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