CPIC Updates

Thank you for attending the PGRN/ClinPGx meeting!

- CE Access from the PGRN/ClinPGx Meeting
  - Contact **pharmedu@stjude.org**

- To add CPIC meeting to your calendar:
  - https://cpicpgx.org/member-resources/
  - Has link to add meeting

Advancing Clinical Pharmacogenomics Worldwide Through the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Kelly E. Caudle[1,*], Michelle Whirl-Carrillo[2], Mary V. Relling[1], James M. Hoffman[1], Roseann S. Donnelly[1,3], Cyrine E. Haidar[1], Melissa S. Bourque[1], Samantha Frear[3], Li Gong[2], Katrin Sangkuhl[2], Ryan Whaley[2] and Teri E. Klein[4]

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Table 1 CPIC by the numbers

	Numbers	Applicable link
CPIC members		https://cpicpgx.org/members/
Members[a]	781	
Clinician	370	
Clinician–Scientist	91	
Researcher	179	
Other	171	
Institutions	588	
Countries	52	
CPIC guidelines	28	https://cpicpgx.org/guidelines/
Unique genes	34	
Unique drugs	164	
Final CPIC level[b]		https://cpicpgx.org/genes-drugs/
A	96	
B	15	
C	204	
Provisional CPIC Level[b]		https://cpicpgx.org/genes-drugs/
A	3	
A/B	8	
B	17	
B/C	56	
C	67	
C/D	5	
D	102	

Table 2 CPIC guidelines' citations, views, and guidelines implemented by CPIC members

CPIC Guideline	Years Published	Citations	Total Views[a]	% (*n*) of CPIC member survey respondents implementing guideline[b]	Guideline website link
TPMT, NUDT15, and Thiopurines[19]	2011 /2013/2018	1,277	160,316	79% (73)	https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/
CYP2C19 and Clopidogrel[20]	2011/2013/2022	1,487	252,972	78% (72)	https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/
CYP2C9, VKORC1, CYP4F2, and Warfarin[21]	2011/2016	1,071	144,990	52% (48)	https://cpicpgx.org/guidelines/guideline-for-warfarin-and-cyp2c9-and-vkorc1/
HLA-B and Abacavir[16]	2012	304	60,588	51% (47)	https://cpicpgx.org/guidelines/guideline-for-abacavir-and-hla-b/
CYP2D6, OPRM1, COMT, and Opioids[22]	2012/2014/2020	1,185	216,403	67% (62)	https://cpicpgx.org/guidelines/guideline-for-codeine-and-cyp2d6/
SLCO1B1, ABCG2, CYP2C9, and Statins[23]	2012/2014/2022	878	198,611	60% (55)	https://cpicpgx.org/guidelines/cpic-guideline-for-statins/
HLA-B and Allopurinol[24]	2013	202	50,914	33% (30)	https://cpicpgx.org/guidelines/guideline-for-allopurinol-and-hla-b/
CYP2D6, CYP2C19, and Tricyclic Antidepressants[25]	2013/2016	907	187,171	62% (57)	https://cpicpgx.org/guidelines/guideline-for-tricyclic-antidepressants-and-cyp2d6-and-cyp2c19/

CPIC authors

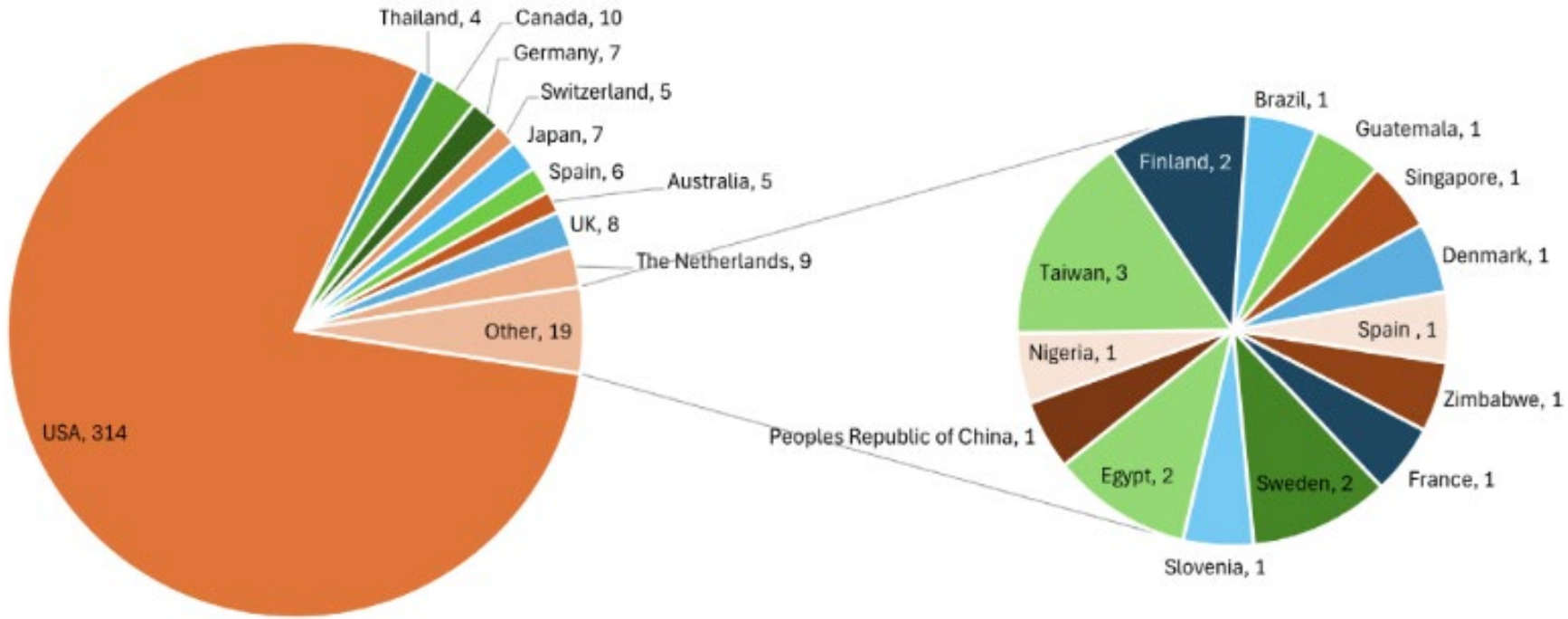
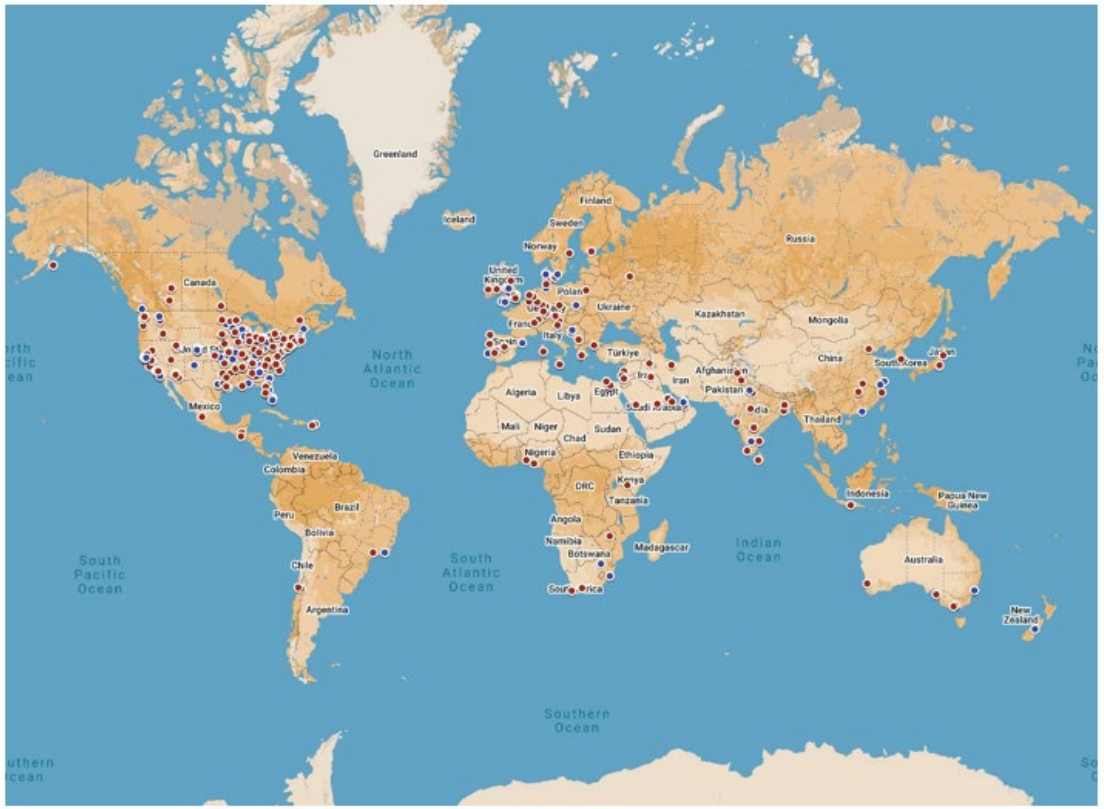


Figure 3 Current CPIC authors by country.

CPIC is a global organization and has global impact

CPIC Members



Legend

Academia/Research

Industry

>780 members (clinicians and scientists)

>590 institutions

52 countries

Guideline authors are international

- 23% of authors are from outside the US
- Span all Europe, Asia, South America, Africa, Australia

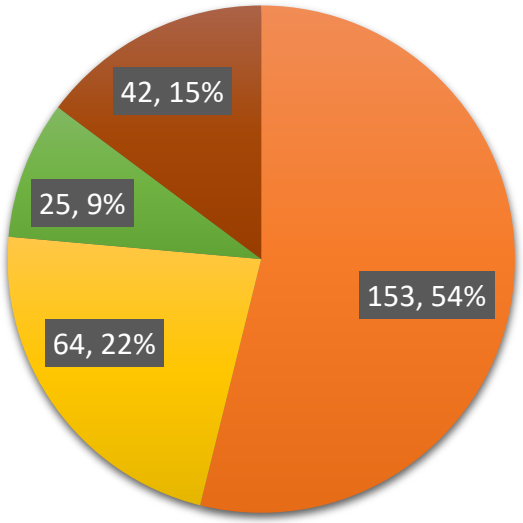
CPIC®

CPIC guidelines are extensively used in peer-reviewed published pharmacogenomic implementation projects

682 publications

Jan. 2019-Jan. 2024
"pharmacogenomics" OR pharmacogenetics"
AND "implementation"

284 publications



Excluded:

- Not implementation related or review (n=355)
- Gene/drug pair without CPIC guideline (n=27)
- Not available for review (n=1)
- Duplicate article (n=2)
- Not in English (n=13)

- 85% (242/284) used CPIC
- 49% (119/242) were outside of US

Caudle, *et al. Clin Pharmacol Ther*. 2025 Jul 18. doi: 10.1002/cpt.70005. Online ahead of print.

Supplement:
CPIC Survey 2012 versus 2024

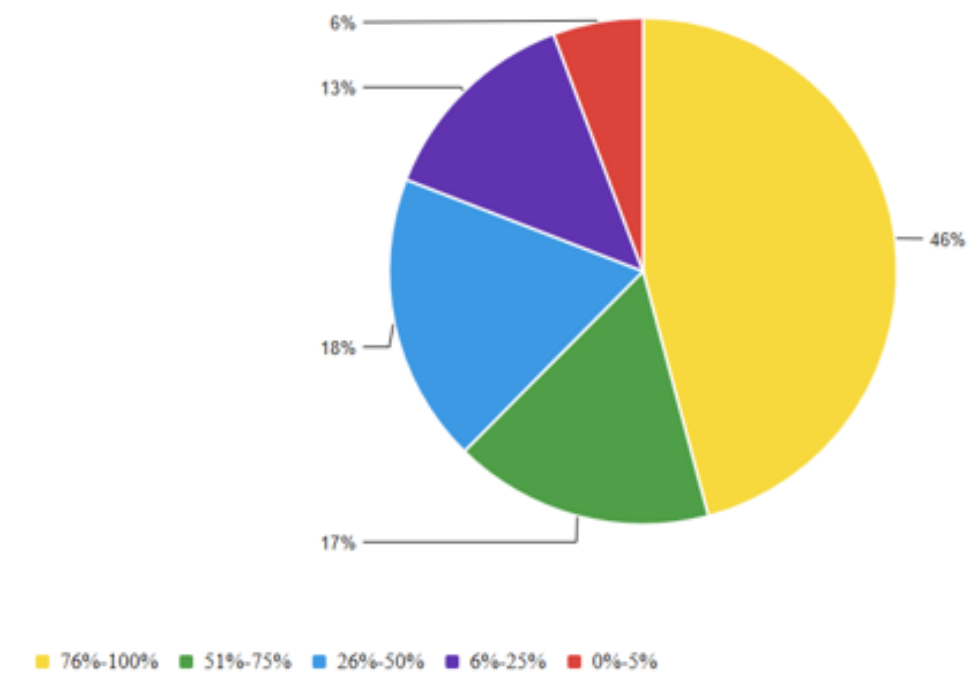


FIGURE S2. PERCENTAGE OF TIME SPENT IN PHARMACOGENOMICS (2024 RESULTS; n=157)

TABLE S1. DEMOGRAPHICS

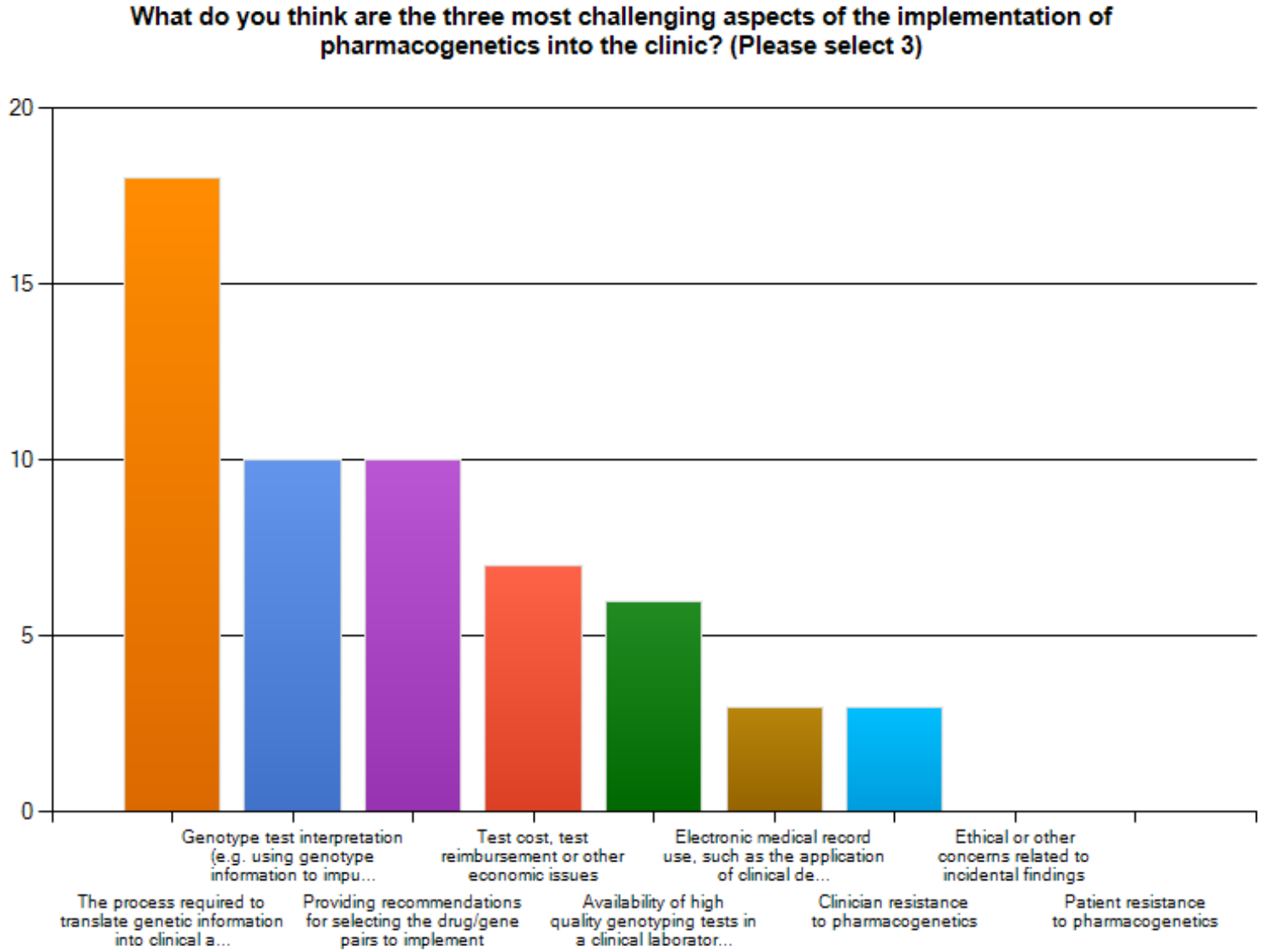
Survey Year	**2012**	**2024**
Background	**% (n)**	**% (n)**
Practicing pharmacist	16% (6)	52% (84)
PharmD	32% (12)	53% (85)
Academic research	84% (32)	36%(58)
PhD	58% (22)	28% (46)
Clinical laboratory professional	3% (1)	15% (24)
Industry	5% (2)	11% (17)
MD	29% (11)	9% (14)
Practicing physician	21% (8)	7% (11)
Government/regulatory	5% (2)	6% (9)
Student	5% (2)	1% (2)
Genetic counselor	NA	4% (6)
Computer scientist/bioinformatician	NA	4% (6)
Other	NA	6% (10)
Survey Year	**2014**	**2024**
Workplace Setting	**% (n)**	**% (n)**
For profit hospital or clinic	4% (2)	3% (4)
Nonprofit or academic hospital or clinic	52% (25)	50% (79)
Reference/clinical laboratory	13% (6)	3% (5)
Educational or research resource	19% (9)	1% (2)
University	38% (18)	21% (33)
Research or clinical institute	19% (9)	3% (5)
Laboratory test interpretation service	17% (8)	5% (8)
Commercial laboratory	NA	4% (7)

2011 survey:

95% of respondents selected:
"process required to translate genetic information into clinical actions"

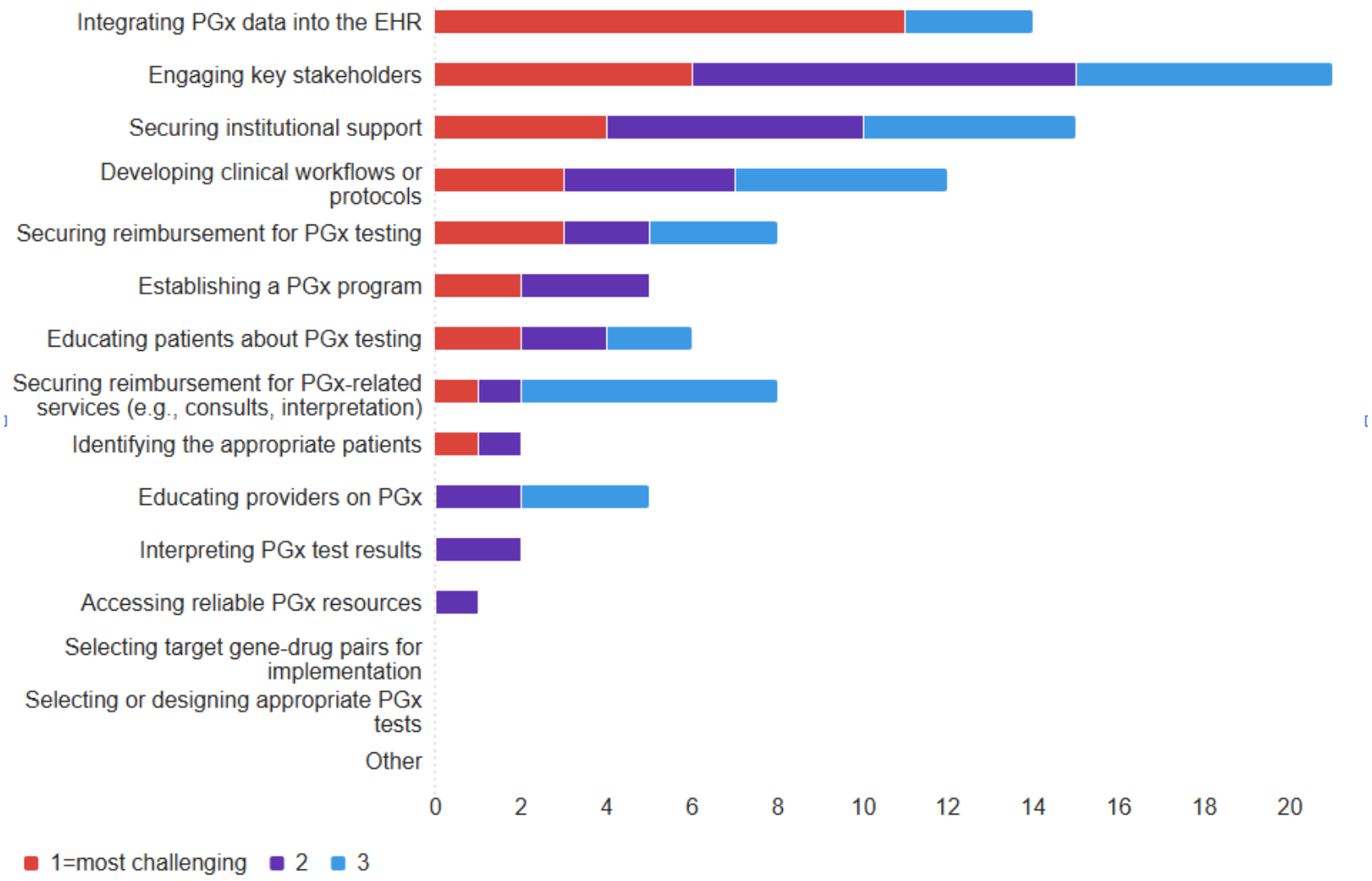
Next 2 responses:

- Genotype test interpretation (e.g. using genotype information to impute phenotype)
- Providing recommendations for selecting the drug/gene pairs to implement



Barriers have shifted to more implementation related barriers

Pre-meeting survey: Barriers ranked from most challenging to least challenging



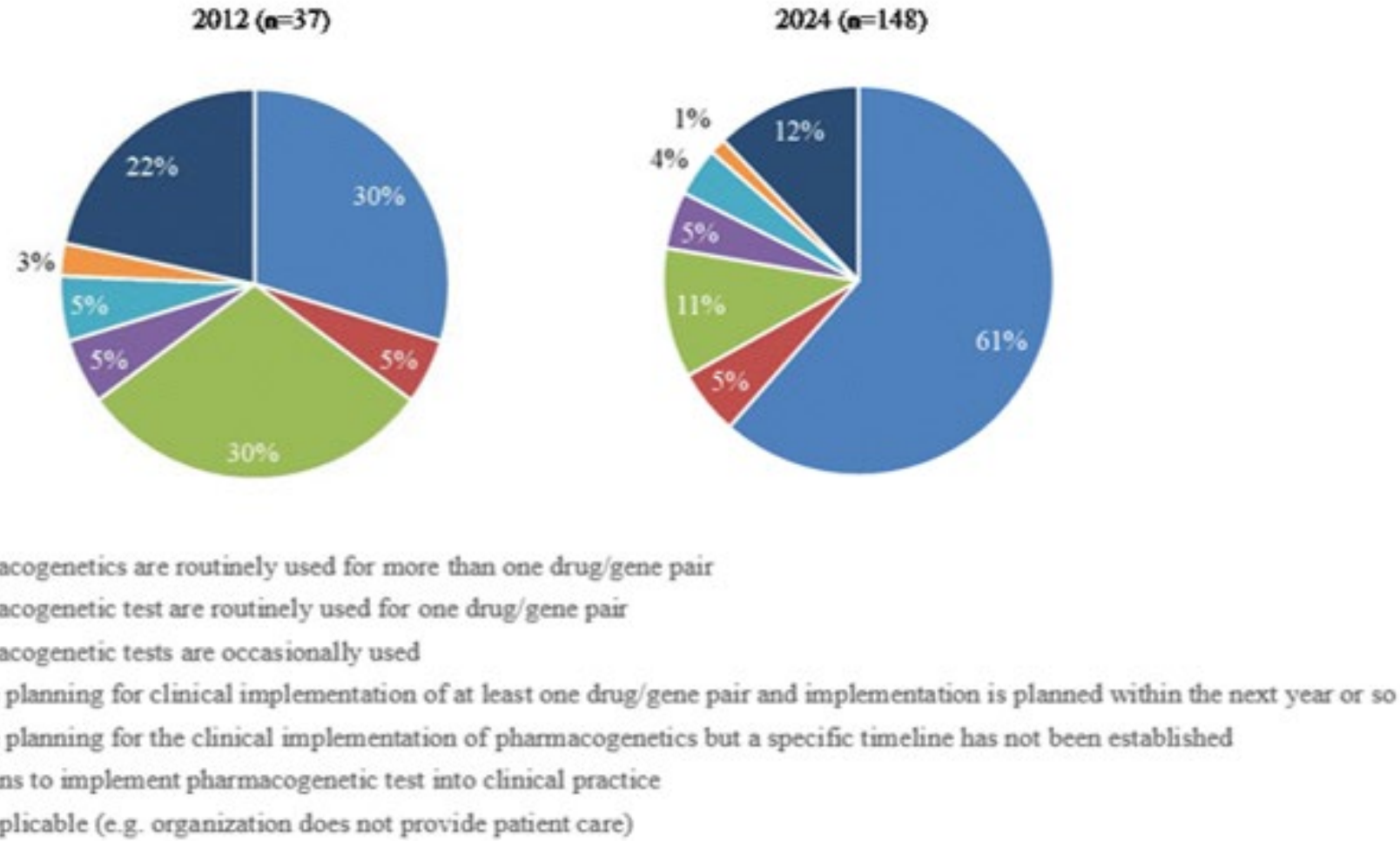


FIGURE S4. LEVEL OF PHARMACOGENOMICS ADOPTION BY CPIC MEMBER INSTITUTIONS (CPIC MEMBER SURVEY 2012 TO 2024)

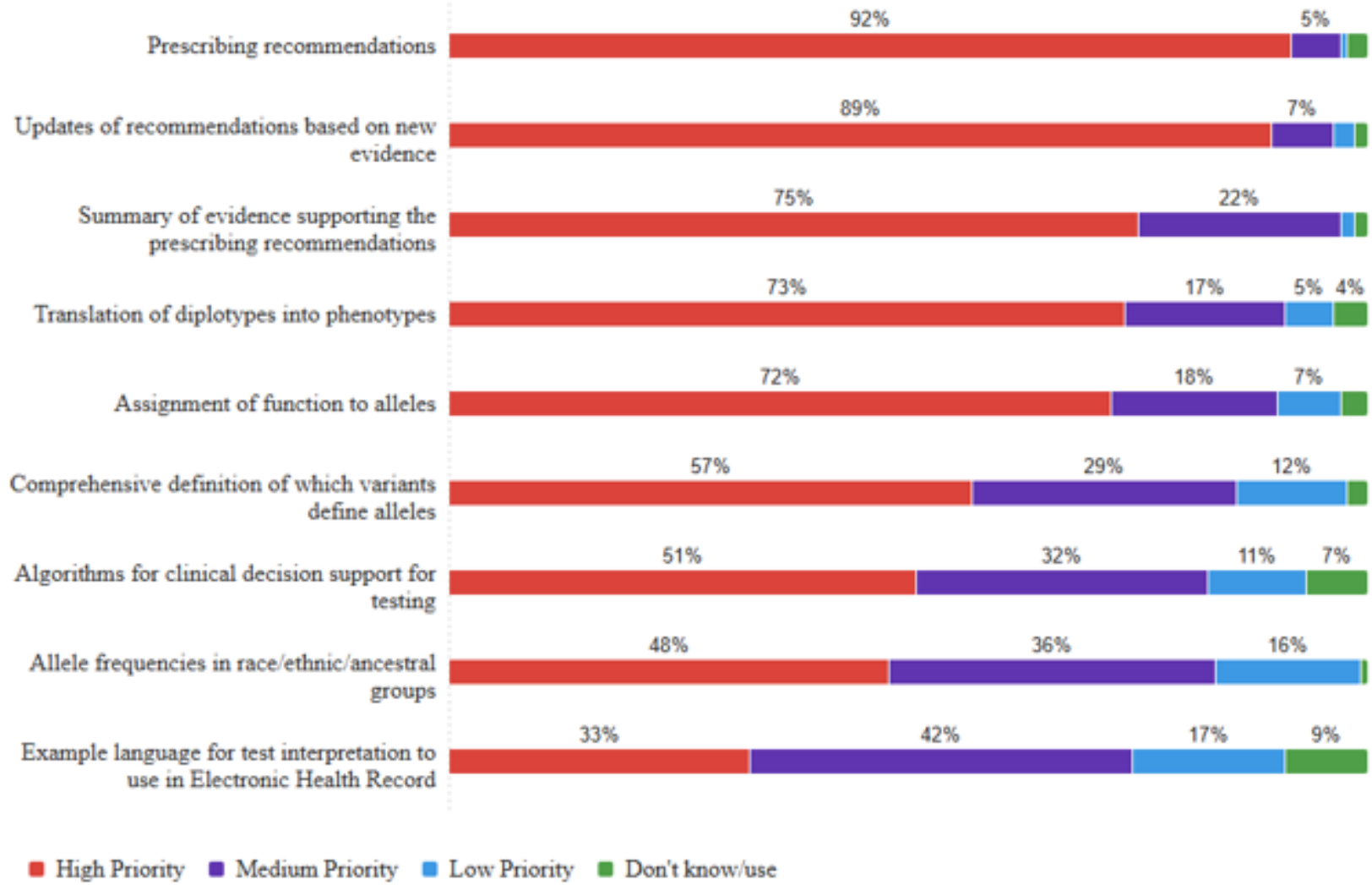


FIGURE S5. CPIC GUIDELINE ELEMENTS PRIORITY (CPIC MEMBER SURVEY 2024, n=132)

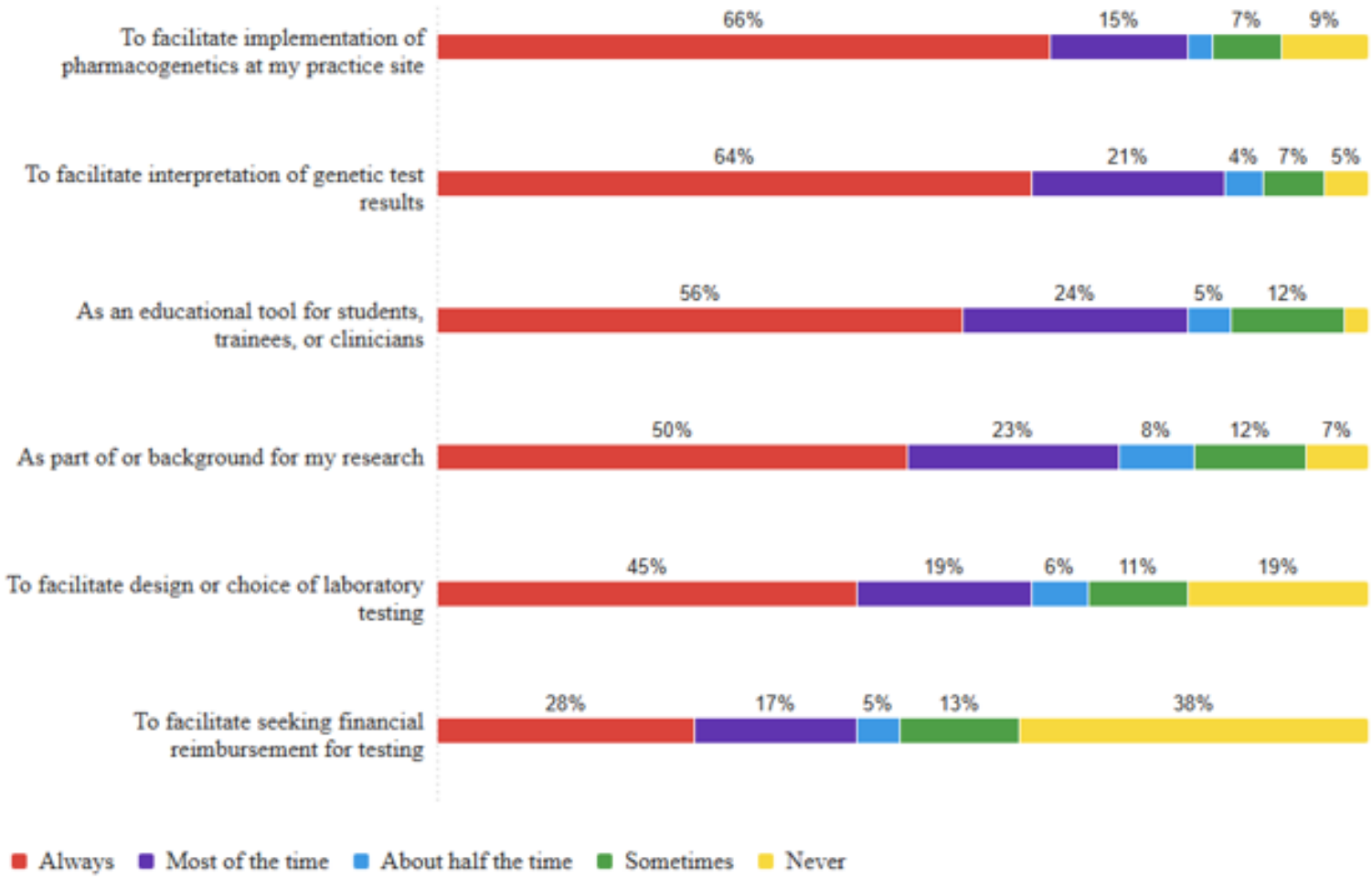


FIGURE S6. CPIC GUIDELINE USE OVER THE PAST 5 YEARS (CPIC MEMBER SURVEY, n=149)

Published 29 guidelines and 16 updates, covering 35 genes and > 160 drugs

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- *TPMT, NUDT15*
  - Mercaptopurine, thioguanine, azathioprine
- *CYP2D6*
  - Codeine, tramadol, hydrocodone, tricyclic antidepressants (TCAs), tamoxifen, selective serotonin reuptake inhibitors (SSRIs), ondansetron, tropisetron, atomoxetine, vortioxetine
  - Beta-blockers (CPIC level B or C)
  - Methadone, oxycodone (CPIC level C)
- *CYP2C19*
  - TCAs, clopidogrel, voriconazole, SSRIs, proton pump inhibitors (PPIs), vortioxetine (CPIC level C)
- *VKORC1* and *CYP4F2*
  - Warfarin
- *CYP2C9*
  - Warfarin, phenytoin, NSAIDs (nonsteroidal anti-inflammatory drugs), fluvastatin, aspirin (CPIC level C)
- CYP2C8
  - NSAIDs
- *HLA-B and HLA-A*
  - Allopurinol, carbamazepine, oxcarbazepine, abacavir, fosphenytoin, phenytoin
- *CFTR*
  - Ivacaftor
- *DPYD*
  - Fluorouracil, capecitabine, tegafur
- *G6PD*
  - 48 drugs
- *UGT1A1*
  - Atazanavir
- *SLCO1B1*
  - Statins
- *IFNL3 (IL28B)*
  - Interferon
- *CYP3A5*
  - Tacrolimus
- *CYP3A4/5*
  - Statins (CPIC level C)

https://cpicpgx.org/guidelines/

- *CYP2B6*
  - Efavirenz, sertraline (CPIC level B)
  - Methadone (CPIC level C)
- *RYR1, CACNA1S*
  - Inhaled anesthetics
- *mtRNR1*
  - Aminoglycosides
- *ABCG2*
  - Rosuvastatin
- *NAT2*
  - Hydralazine
- *OPRM1* and *COMT*
  - Opioids (CPIC level C)
- *HMGCR*
  - Statins (CPIC level C)
- *SLC6A4* and *HTR2A*
  - SSRIs, serotonin/norepinephrine reuptake inhibitors (SNRIs), vortioxetine, vilazodone (CPIC level C)
- *ADRB1, ADRB2, ADRA2C, GRK4,* and *GRK5*
  - Beta-blockers (CPIC level C)

CPIC guidelines help clinicians translate from genotype to phenotype to clinical recommendation

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GENOTYPE

TPMT*3A/*3A

Table 1

PCEP

PHENOTYPE

TPMT Poor Metabolizer

Table 2

CPGP

RECOMMENDATION

Decrease dose

STRONG

PCEP: Pharmacogenomics curation exert panel; CPGP: Clinical practice guideline panel

Scientific staff at Stanford ClinPGx

- Li Gong, PhD

- Katrin Sangkuhl, PhD

- Caroline Thorn, PhD

- Evangelia Eirini Tsermpini, PhD

CPIC guidelines in progress

- *NAT2*/hydralazine-published!
- *TPMT-NUDT15*/thiopurines-submitting today!
- *CYP2D6*/5-HT3s-drafted; will circulate to members soon
- Antipsychotics-almost done with recommendations; started drafting

CPIC guidelines in progress

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- *CYP2D6*/5-HT3s-drafted; will circulate to members soon
- Antipsychotics-almost done with recommendations; started drafting
- CYP3A/tacrolimus-working on recommendations
- *DPYD*/fluoropyrimidines
- *UGT1A1*/irinotecan-evidence review underway
- HLA guideline-recruiting authors now

HLA guideline

Antibiotics/Ant-infectives

- Sulfonamide antibiotic (DRESS and SJS/TEN)
- Dapsone hypersensitivity
- Vancomycin (DRESS)
- Nevirapine (DRESS and SJS/TEN)
- Abacavir Hypersensitivity

Anti-epileptic drugs (DRESS and SJS/TEN)

- Carbamazepine/oxcarbazepine
- Phenytoin
- Lamotrigine
- Zonisamide

Allopurinol (DRESS and SJS/TEN)

Miscellaneous (DRESS and SJS/TEN)

- Including other antibiotics (fluoroquinolone), anti-neoplastic drugs, anti-infectives, sulfasalazine.

Drug-induced liver injury

- Antibiotics (amoxicillin-clavulanate would be the main one)

Miscellaneous phenotype

- Anaphylaxis, thyroid disease, leucopenia etc

CPICs guideline development process aligns with the NAM's guidelines we can trust standards

Guideline nominated; discussed on CPIC call and prioritized

Authors identified and approved by the Steering Committee

Guideline started: evidence review, conference calls, refine drugs/genes, revise as needed

Draft guideline discussed on CPIC call; posted on CPIC site for comment; submitted for publication

Final guideline posted on CPICpgx.org; updated on site as needed

Guideline revised if prescribing recommendations must change

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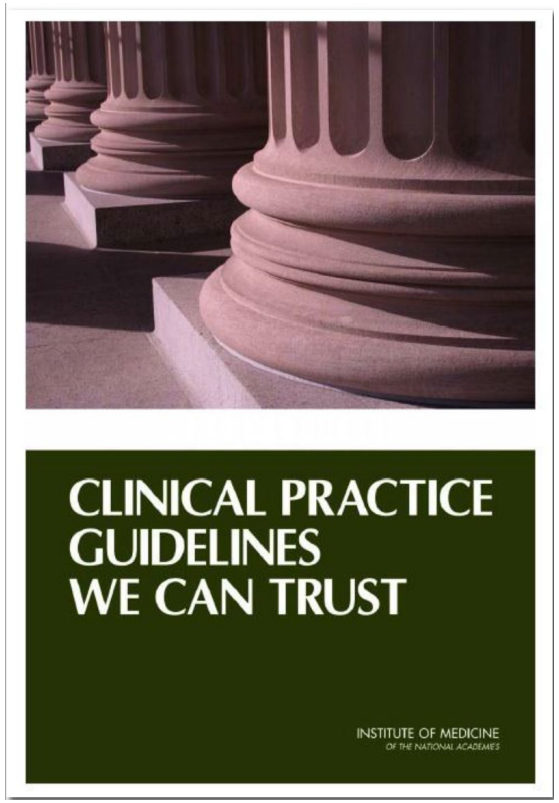

Caudle et al, *Curr Drug Metab*. 2014 Feb;15(2):209-17.

Expert Selection and CPIC Steering Committee Approval

Author group formation process

- Begins when new guideline or guideline update is approved by CPIC members and CPIC Steering Committee
- Authors are identified through self-nomination or nomination by CPIC Steering Committee or colleague
- CPIC Steering Committee must approve authorship plans for each CPIC guideline and at each update
- Authors can be added later in the process with approval of senior author and CPIC Steering Committee
- Author group includes at least one CPIC staff and Stanford member

Desirable characteristics

- Multidisciplinary author group (clinicians and scientists)
- Laboratory/testing expertise
- International representation
- Expertise in clinical pharmacogenetics or specific topic area of guideline

Requirements

- Expertise or publications on guideline topic
- Signed CPIC Publication of MOU and conflict of interest (COI) disclosure

COI

- Senior author, first author and majority of the author group should not have COIs
- Transparent to all authors and readers and published in manuscript
- If new COI arises during guideline process, contact CPIC staff on guideline

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Future CPIC work

- Need to update multiple guidelines
  - CYP2C19/voriconazole
  - TCA guideline
  - CYP2D6/atomoxetine
  - CFTR
  - Others
- Expanded scope?
  - New drugs with PGx labeling information without many published data
  - Disease causing variants with some PGx implications

PCEP Standard Operating Procedure

- Expert selection and training
- Inclusion of Alleles
- Evidence collection and review
- Summarizing the Evidence
- Assigning allele clinical function and strength of evidence
- Translating diplotypes to phenotypes
- Re-evaluations and updates

Expert Selection and Approval by CPIC Steering Committee

Identification

- Process begins when a new guideline or guideline update is approved
- Self nomination or nomination by colleagues
- Request by CPIC Steering Committee
- Includes trained CPIC staff assisting with guideline development

Desirable characteristics

- Multidisciplinary committee (scientists and clinicians)
- International representation
- Leader or senior individual in the specific topic area of the guideline

Requirements

- Advanced degree (MD, PharmD, PhD)
- Expertise or publications on the guideline topic
- Signed CPIC Publication of MOU (agreement to follow CPIC SOPs—including Training)
- Signed conflict of interest disclosure

Management of Conflict of Interest

- Guided by the Institute of Medicine Standards for Developing Trustworthy Clinical Practice Guidelines
- Made transparent to all authors and readers, published in the manuscript
- Senior author, first author, and majority of the writing group should not have a conflict of interest

CPIC Guidelines are highly collaborative

PCEPs in process

- PCEP overview paper- in review
- NAT2-submitting paper soon (tables available online)
  - https://cpicpgx.org/guidelines/cpic-guideline-for-hydralazine-and-nat2/
  - https://www.clinpgx.org/
- TPMT/NUDT15-drafted; submitting soon
- DPYD-underway
- CYP3A
- SLCO1B1
  - https://cpicpgx.org/guidelines/cpic-guideline-for-statins/

CYP2D6 and 5-HT_3 Receptor Antagonists update

- **Claire Moore**
- Melissa S. Bourque
- Andreas Halman
- José A. G. Agúndez
- Cynthia A. Prows
- Keiko Hikino
- Matthias Schwab
- Carolyn J. Oxencis
- Dharmisha Chauhan
- M.H.M. Diekstra
- Susie Long
- Gillian C. Bell
- Andrea Gaedigk
- Michelle Whirl-Carrillo
- Teri Klein
- Kelly E. Caudle
- **Rachel Conyers**

Table 2. Dosing Recommendations for ondansetron and tropisetron based on *CYP2D6* Phenotype

Phenotype	Activity score	Implications	Recommendations	Classifications of recommendations[a]
CYP2D6 ultrarapid metabolizer	>2.25	Increased metabolism to less active compounds when compared to NMs and is associated with decreased response to ondansetron and tropisetron (e.g., vomiting).	Select alternative drug not predominantly metabolized by CYP2D6 (i.e., granisetron)[b,c]	Moderate
CYP2D6 normal metabolizer	1.25≤x≤2.25	Normal metabolism of ondansetron and tropisetron	Initiate therapy with recommended starting dose.	Strong
CYP2D6 intermediate metabolizer	0<x<1.25	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype.	No recommendation	No recommendation
CYP2D6 poor metabolizer	0	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype.	No recommendation	No recommendation
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

n/a, not applicable.

[a] Rating scheme described in **Supplemental Materials**

[b] Drug-drug interactions and other patient characteristics (e.g., age, renal function, and liver function) should be considered when selecting alternative therapy.

[c] Dolasetron, palonosetron, and ramosetron are also metabolized by CYP2D6. Limited evidence is available regarding the utilization of *CYP2D6* genetic variation to guide use of these drugs. See Supplement Tables S3 and S4.

Supplemental table S3: Dosing Recommendations for Dolasetron Based on *CYP2D6* Phenotype

Phenotype	Activity score	Implications	Recommendations	Classifications of recommendations[a]
CYP2D6 ultrarapid metabolizer	>2.25	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype.	No recommendation	Weak
CYP2D6 normal metabolizer	1.25≤x≤2.25	Normal metabolism	Initiate therapy with recommended starting dose.	Strong
CYP2D6 intermediate metabolizer	0<x<1.25	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype.	No recommendation	No recommendation
CYP2D6 poor metabolizer	0	Increased (hydro)dolasetron AUC, half-life and/or Cmax compared to normal metabolizers; however, there is insufficient evidence that demonstrates clinical impact.	No recommendation	Moderate
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

n/a, not applicable.

[a]Rating scheme described in **Supplemental Materials**

Supplemental table S4. Dosing Recommendations for Palonosetron and Ramosetron Based on *CYP2D6* Phenotype

Phenotype	Activity score	Implications	Recommendations	Classifications of recommendations[a]
CYP2D6 ultrarapid metabolizer	>2.25	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype.	No recommendation	No recommendation
CYP2D6 normal metabolizer	1.25≤x≤2.25	Normal metabolism	Initiate therapy with recommended starting dose.	Strong
CYP2D6 intermediate metabolizer	0<x<1.25	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype.	No recommendation	No recommendation
CYP2D6 poor metabolizer	0	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype.	No recommendation	No recommendation
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

n/a, not applicable.
[a]Rating scheme described in **Supplemental Materials**

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CPIC™
Clinical Pharmacogenetics Implementation Consortium

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- And:
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