PharmCAT: A Tool for Pharmacogenomics Implementation

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May 2, 2017

Geisinger PharmGKB Stanford

28 CPIC guideline publications* (including updates)

- 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

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*https://cpicpgx.org/publications/

Motivation for PharmCAT

To automate the annotation of .vcf files with the appropriate haplotypes or diplotypes from the CPIC guideline genes, and generate a report with the corresponding CPIC guideline prescribing recommendations

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Motivation for PharmCAT - #1

95-96% of individuals have one or more genetic variants in important PGx genes

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Genetic Variation Among 82 Pharmacogenes: The PGRNseq Data From the eMERGE Network

WS Bush[1], DR Crosslin[2], A Owusu-Obeng[3], J Wallace[4], B Almoguera[5], MA Basford[6], SJ Bielinski[7], DS Carrell[8], JJ Connolly[5], D Crawford[1], KF Doheny[9], CJ Gallego[2], AS Gordon[2], B Keating[5], J Kirby[6], T Kitchner[10], S Manzi[11], AR Mejia[3], V Pan[12], CL Perry[11], JF Peterson[6], CA Prows[13], J Ralston[8], SA Scott[3], A Scrol[8], M Smith[12], SC Stallings[6], T Veldhuizen[7], W Wolf[11], S Volpi[14], K Wiley[14], R Li[14], T Manolio[14], E Bottinger[3], MH Brilliant[10], D Carey[15], RL Chisholm[12], CG Chute[9], JL Haines[1], H Hakonarson[5], JB Harley[16], IA Holm[17], IJ Kullo[7], GP Jarvik[2], EB Larson[8], CA McCarty[10], MS Williams[15], JC Denny[6], LJ Rasmussen-Torvik[12], DM Roden[6] and MD Ritchie[15]

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Received 6 October 2015; accepted 4 February 2016; advance online publication 00 Month 2016. doi:10.1002/cpt.350

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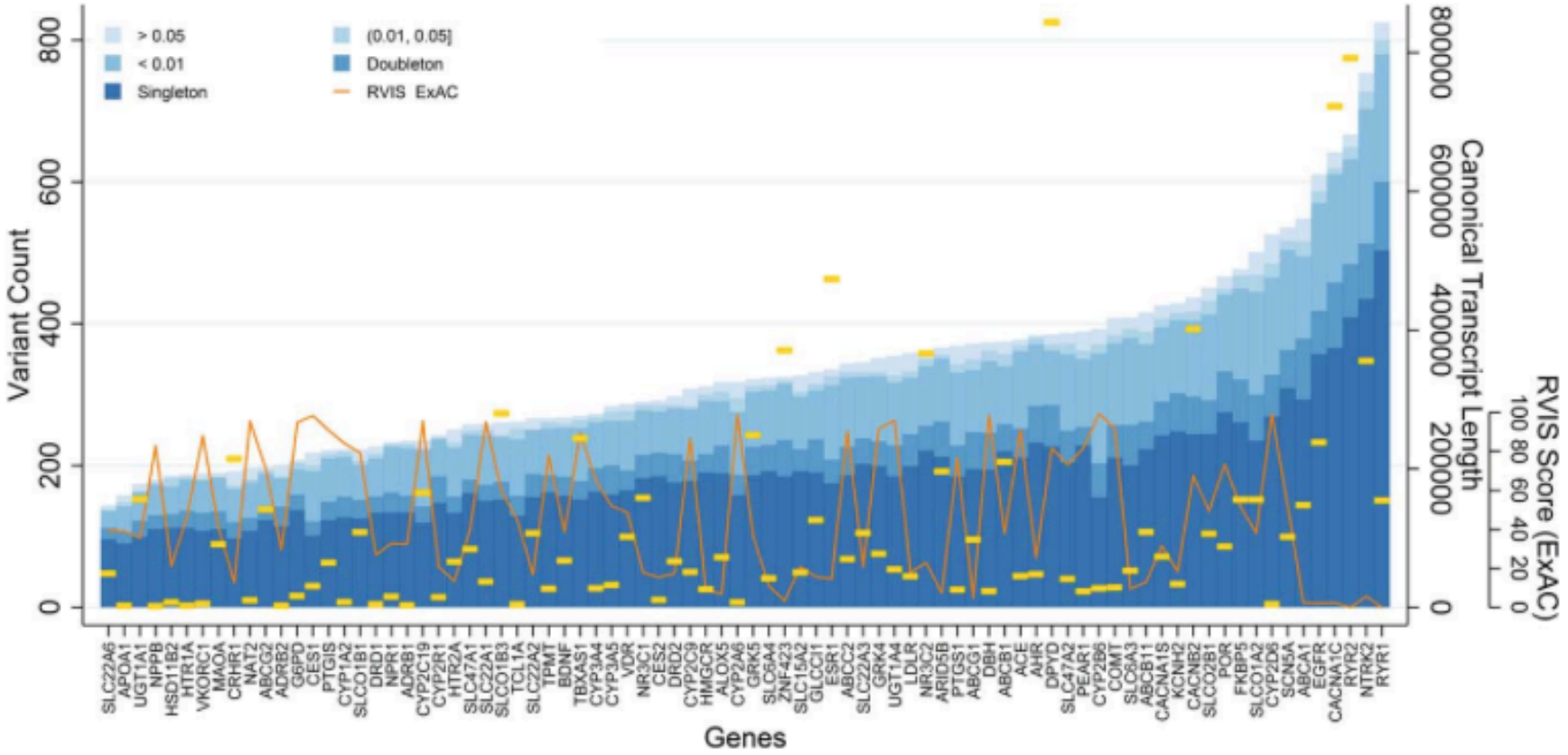

Figure 1 Allelic spectrum of eMERGE-PGx variants. Counts of genomic variants mapping to the canonical transcript of PGRNseq captured genes are plotted by frequency class (over all samples) by gene (x-axis) in ascending order. Gold horizontal lines indicate the size of the canonical transcript in base-pairs. The inset line plot is a percentile rank of genic intolerance (RVIS) scores computed using the ExAC dataset.

~96% of the 5000 subjects has one or more variants in CPIC level-A genes

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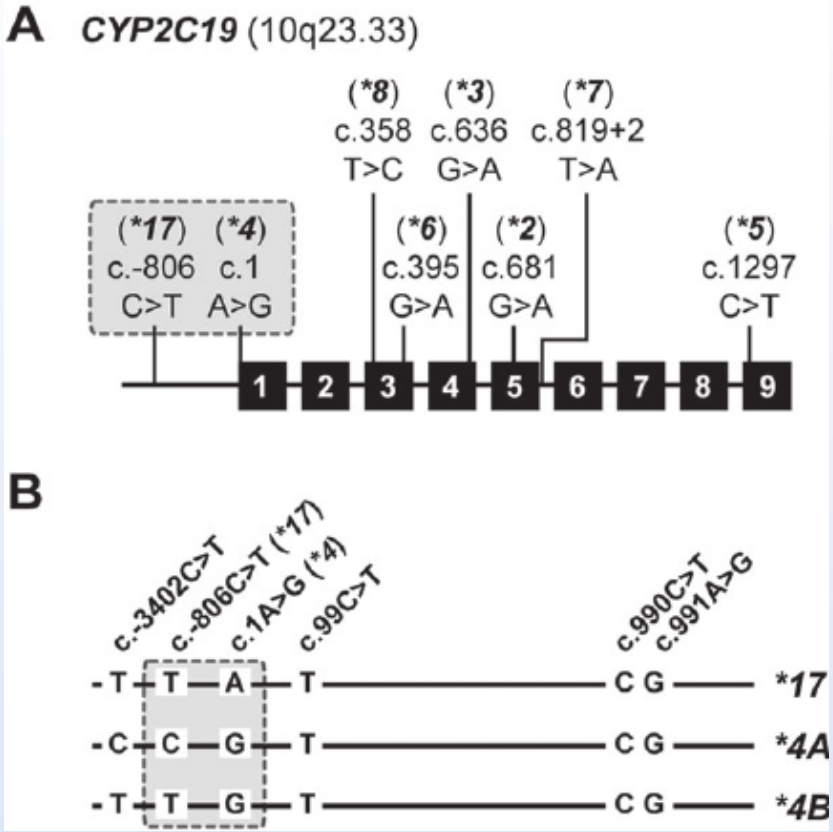
Motivation for PharmCAT - #2



Extracting genomic variants and assigning haplotypes (including star-alleles) from genetic data is challenging

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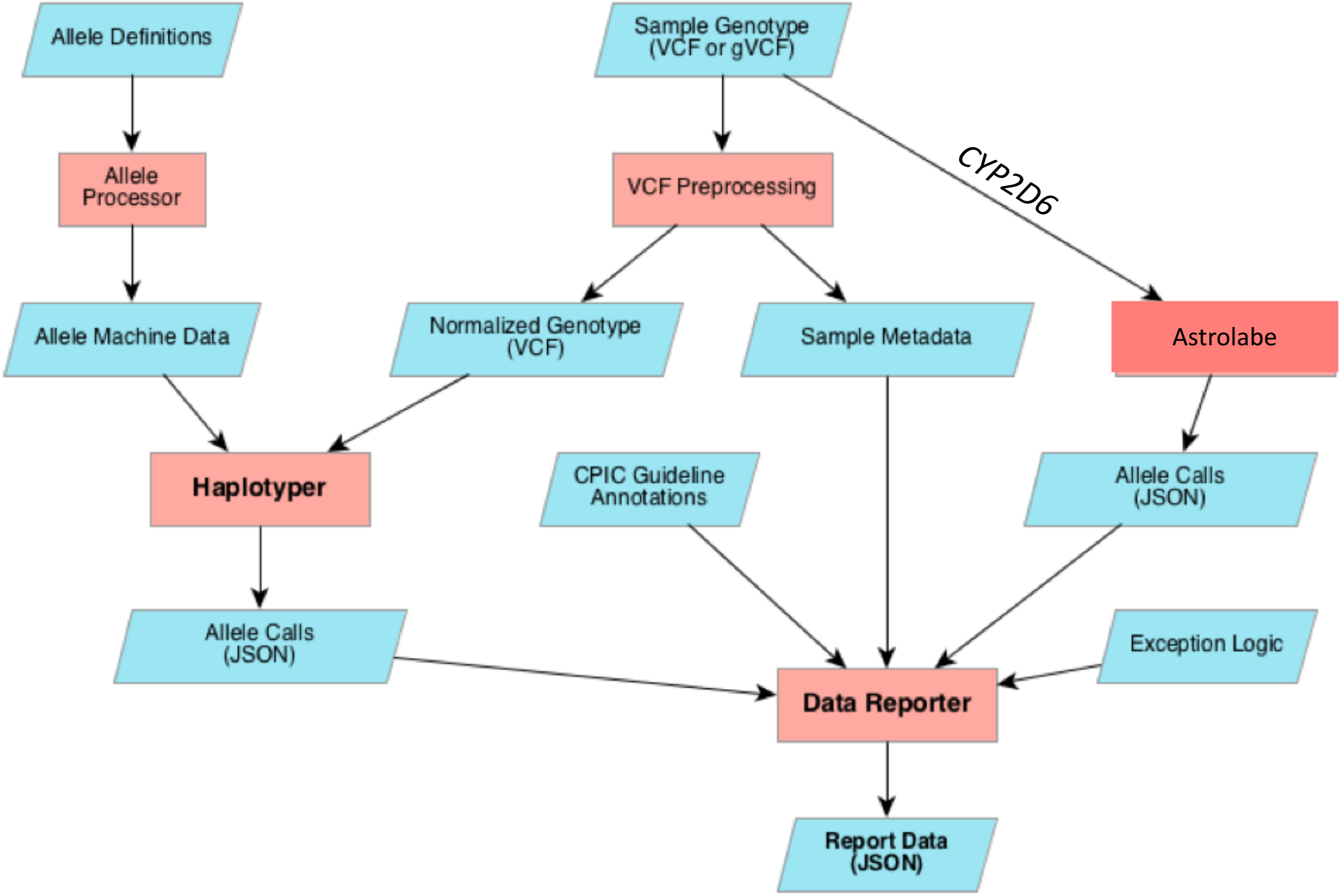
PharmCAT – a Community Effort

- Community stake-holders
  - PGRN, CPIC, ClinGen, eMERGE, P-STAR, PharmGKB
- Rules of engagement
  - MPL 2.0 license
  - Code posted in github – updates need to be contributed
- Several collaborative meetings
  - Meeting 1 – March, 2016: think tank
  - Meeting 2 – April, 2016: Hackathon – for programmers
  - Meeting 3 – May, 2016: dissemination, future planning
  - Meeting 4 – January, 2017: evaluation, coding, planning

PharmCAT Workflow



CPIC Guidelines

PharmCAT version 1

- These genes are in process for release in PharmCAT version 1.0
  - *CFTR, CYP2C19, CYP2C9, CYP2D6, CYP3A5, CYP4F2, DPYD, IFNL3, SLCO1B1, TPMT, UGT1A1, VKORC1*
- These genes are more difficult and require more work: *G6PD, HLA-B, CYP2D6**
- *CYP2D6* haplotype calls are coming from Astrolabe
  - Integrated into PharmCAT
  - Will require user license to Astrolabe
  - JSON calls join Data Reporter for PharmCAT report

CPIC Haplotype Table – *CYP2C19* example

GENE: CYP2C19	5/27/16															
	Nucleotide change to gene from http://www.cypalleles.ki.se/cyp2c19.htm	-2030C>T	-2020C>A	-1439T>C	-1041G>A	-806C>T	-13G>A	1A>G	7C>T	10T>C	50T>C	55A>C	83A>T	151A>G	12401C>T	12416C>T
	Effect on protein (NP_000760.1)	5' region	5' region	5' region	5' region	5' region	5' region	M1V	P3S	F4L	L17P	I19L	K28I	S51G	R73C	H78Y
	Position at NC_000010.11 (Homo sapiens chromosome 10, GRCh38.p2)	g.94760676C>T	g.94760686C>A	g.94761267T>C	g.94761665G>A	g.94761900C>T	g.94762693G>A	g.94762706A>G	g.94762712C>T	g.94762715T>C	g.94762755T>C	g.94762760A>C	g.94762788A>T	g.94762856A>G	g.94775106C>T	g.9477512 1C T
	Position at NG_008384.2 (CYP2C19 RefSeqGene; forward relative to chromosome)	g.2971C>T	g.2981C>A	g.3562T>C	g.3960G>A	g.4195C>T	g.4988G>A	g.5001A>G	g.5007C>T	g.5010T>C	g.5050T>C	g.5055A>C	g.5083A>T	g.5151A>G	g.17401C>T	g.17416C>T
	rsID	rs113164681	rs111490789	rs17878739	rs7902257	rs12248560	rs367543001	rs28399504	rs367543002	rs367543003	rs55752064	rs17882687			rs145328984	
CYP2C19 Allele	Allele Functional Status															
*1	Normal function	C	C	T	G	C	G	A	C	T	T	A	A	A	C	C
*2	No function															
*3	No function															
*4A	No function							G								
*4B	No function					T		G								
*5	No function															
*6	No function															
*7	No function															
*8	No function															
*9	Decreased function															
*10	Decreased function															
*11	Normal function															
*12	Unknown function															
*13	Normal function															
*14	Unknown function										C					
*15	Normal function											C				
*16	Decreased function															
*17	Increased function					T										
*18	Normal function															
*19	Decreased function													G		
*22	No function															
*23	Unknown function															

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CPIC Guideline – *CYP2C19* example

CPIC Guideline for sertraline and CYP2C19

The CPIC Dosing Guideline for the selective serotonin reuptake inhibitor sertraline recommends to consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19 for CYP2C19 poor metabolizers.

Annotations for CYP2C19:*1/*2

Type	Annotation
Implications	Reduced metabolism when compared to extensive metabolizers.
Metabolizer Status	Intermediate metabolizer (~18-45% of patients)
Phenotype (Genotype)	An individual carrying one normal function allele or one increased function allele and one no function allele. *The predicted metabolizer phenotype for the*2/*17 genotypes is a provisional classification. The currently available evidence indicates that the CYP2C19*17 increased function allele is unable to completely compensate for the no function CYP2C19*2.*
Recommendations	Initiate therapy with recommended starting dose.
Classification of Recommendation	Strong

For full guideline see https://cpicpgx.org

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Haplotyper– *CYP2C19* example

CYP2C19

- *1/*2 (40)

Definition Position	94760676	94760686	94761267	94761665	94761900	94762693	94762706	94762712	94762715	94762755	94762760	94762788	94762856	94775106	94775121	94775160	94775185	94775367	94775416	94775453	94775489	94775
	rs113164681	rs111490789	rs17878739	rs7902257	rs12248560	rs367543001	rs28399504	rs367543002	rs367543003	rs55752064	rs17882687			rs145328984		rs118203756		rs12769205	rs41291556	rs72552267	rs17884712	rs5897
VCF Position	94760676	94760686	94761267	94761665	94761900	94762693	94762706	94762712	94762715	94762755	94762760	94762788	94762856	94775106	94775121	94775160	94775185	94775367	94775416	94775453	94775489	94775
VCF REF,ALTs	C	C	T	G	C	G	A	C	T	T	A	A	A	C	C	G	A	A	T	G	G	G
VCF Call	C|C	C|C	T|T	G|G	C|C	G|G	A|A	C|C	T|T	T|T	A|A	A|A	A|A	C|C	C|C	G|G	A|A	A|A	T|T	G|G	G|G	G|
*1	C	C	T	G	C	G	A	C	T	T	A	A	A	C	C	G	A	A	T	G	G	G
	C	C	T	G	C	G	A	C	T	T	A	A	A	C	C	G	A	A	T	G	G	G
*2	C	C	T	G	C	G	A	C	T	T	A	A	A	C	C	G	A	[AG]	T	G	G	G
	C	C	T	G	C	G	A	C	T	T	A	A	A	C	C	G	A	A	T	G	G	G

- PharmCAT takes the .vcf and the CPIC tables into the Haplotyper
- Combines with the CPIC guidelines to generate reports
  - Intermediate
  - Final

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Intermediate report – *CYP2C19* example

Gene: CYP2C19

Matching Allele Call

All variant positions present so all haplotypes considered in analysis.

Diplotype call: CYP2C19:*1/*2

Warnings (none)

Calls at Positions

Position	RSID	Call
94760676	rs113164681	C|C
94760686	rs111490789	C|C
94761267	rs17878739	T|T
94761665	rs7902257	G|G
94761900	rs12248560	C|C
94762693	rs367543001	G|G
94762706	rs28399504	A|A
94762712	rs367543002	C|C
94762715	rs367543003	T|T
94762755	rs55752064	T|T
94762760	rs17882687	A|A
94762788	None	A|A
94762856	None	A|A
94775106	rs145328984	C|C
94775121	None	C|C
94775160	rs118203756	G|G
94775185	None	A|A
94775367	rs12769205	A|A
94775416	rs41291556	T|T
94775453	rs72552267	G|G
94775489	rs17884712	G|G
94775507	rs58973490	G|G
94780574	rs140278421	G|G
94780579	rs370803989	G|G
94780653	rs4986893	G|G
94781858	rs6413438	C|C

- Generates genotype calls at every relevant position
- Includes missing data calls/no calls

PharmCAT report example

PharmCAT Report [test.cftr.reg_inc]

Sections

Diplotype / Genotype Summary

Genotypes called: 12 / 12

Drugs [a]	Gene	Diplotype or Genotype	Allele Functionality [b]	Phenotype [b]	Uncallable Alleles [c]
ivacaftor	CFTR	F508del(TCT)/G542X	N/A	N/A	yes
amitriptyline **escitalopram** **citalopram** **clomipramine** **clopidogrel** **doxepin** **imipramine** **sertraline** **trimipramine** **voriconazole**	CYP2C19	*2/*2	Two no function alleles	Poor Metabolizer	no
phenytoin **warfarin**	CYP2C9	*2/*3	Two decreased function alleles	Poor Metabolizer	no
amitriptyline **clomipramine** **codeine** **desipramine** **doxepin** **fluvoxamine** **imipramine** **nortriptyline** ondansetron **paroxetine** **trimipramine** tropisetron	CYP2D6†	*3/*4	Two no function alleles	Poor Metabolizer	no

PharmCAT Report [test.cftr.reg_inc]

Sections

[a] *The drugs highlighted in red indicate a CPIC recommendation prescribing change based on the person's listed diplotype/genotype (highlighting is not based on CPIC strength of recommendation). See CPIC recommendation section for the classification of the recommendation and further details. Please note, warfarin and peginterferon alpha/ribavirin are highlighted in blue, see CPIC recommendation section for specific prescribing information. The drug is highlighted when multiple diplotypes are presented if any is assocated with a prescribing change. Please see recommendation section for detailed information.*

[b] *Allele functionality and phenotype terms are based on the CPIC term standardization project, PMID:27441996. Guidelines published prior use the term 'extensive' instead of 'normal' metabolizer. CYP2C19*1/*17 is now classified as rapid metabolizer. Guidelines published prior grouped CYP2C19*1/*17 together with *17/*17 as ultrarapid metabolizer.*

[c] *Indicates alleles not considered for the diplotype calls due to missing variant information, please see Allele calls section. Alleles that could not be considered due to missing input might change the metabolizer phenotype and possible CPIC recommendation.*

† *Check the allele call details for this gene for more details about this call.*

For a full list of disclaimers and limitations see the Disclaimer section.

Diplotype / Genotype Summary

Genotypes called: 12 / 12

Drugs [a]	Gene	Diplotype or Genotype	Allele Functionality [b]	Phenotype [b]	Uncallable Alleles [c]
tacrolimus	CYP3A5†	*1/*7	One normal function allele and one no function allele	Intermediate Metabolizer	no
warfarin	CYP4F2	*1/*1	Two normal function alleles	N/A	no
capecitabine fluorouracil tegafur	DPYD	*1/*1	Two normal function alleles	Normal Metabolizer	yes
peginterferon alfa-2a **peginterferon alfa-2b** **ribavirin**	IFNL3†	rs12979860C/rs12979860C	N/A	N/A	no
simvastatin	SLCO1B1†	rs4149056CC	Two decreased function alleles	Poor Function	no
azathioprine mercaptopurine thioguanine	TPMT†	*1/*1	Two normal function alleles	Normal Metabolizer	no
atazanavir	UGT1A1†	*1/*1	Two normal function alleles	Normal Metabolizer	no
warfarin	VKORC1†	-1639A/-1639A	N/A	N/A	no

Summary

- PharmCAT is a Pharmacogenomics Clinical Annotation Tool
- Developed to automate the .vcf → haplotype → CPIC guideline process
- PharmCAT version 1.0 is in testing
  - Goal to release very soon for community feedback
- PharmCAT reports can then be adapted for local implementation into EHR or patient/provider reports

PharmGKB / PharmCAT

The Pharmacogenomic Clinical Annotation Tool - take genome data, make haplotype calls, get CPIC annotations.

README.md

PharmCAT

Take genome data, make haplotype calls, get CPIC annotations.

Status

Please consider this alpha code.

Acknowledgements

- Teri Klein, Stanford, PharmGKB
- Michelle Whirl-Carrillo, Stanford, PharmGKB
- Ryan Whaley, Stanford, PharmGKB
- Lester Carter, PharmGKB
- Katrin Sangkuhl, PharmGKB
- PGRN participants
- ClinGen participants
- CPIC participants
- P-STAR participants

PharmCAT team: T.E. Klein, M. Whirl-Carrillo, R.M. Whaley, M. Woon, K. Sangkuhl, L.G. Carter, H.M. Dunnenberger, P.E. Empey, A.T. Frase, R.R. Freimuth, A. Gaedigk, A. Gordon, C. Haidar, J.K. Hicks, J.M. Hoffman, M.T. Lee, N. Miller, S.D. Mooney, T.N. Person, J.F. Peterson, M.V. Relling, S.A. Scott, G. Twist, A. Verma, M.S. Williams, C. Wu, W. Yang, M.D. Ritchie

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PharmCAT has been funded in part by the following:
PharmGKB:R24 GM61374; CPIC: R24 GM115264; P-STAR: U01 HL065962