SUPPLEMENTARY MATERIALS

Table S1. Genes, variants, and alleles included on the Vanderbilt University Medical Center pharmacogenomic panel test as of September 2020. For each gene, alleles are assigned *1 if all variant alleles are absent.

Gene	Variants	Alleles
CYP2C9	rs1799853, rs1057910, rs9332131, rs7900194, rs28371685, rs28371686	*1, *2, *3, *5, *6, *8, *11
CYP2C19	rs12248560, rs4244285, rs4986893, rs28399504, rs72552267, rs41291556	*1, *2, *3, *4, *6, *8, *17
CYP2D6†	rs28371706, rs16947, rs59421388, rs1080985, rs35742686, rs3892097, rs1065852, rs28371725, rs5030655, rs5030867, rs5030656, rs5030865(T), rs5030865(A), rs1135840, rs5758550	*1, *2, *2A, *3, *4, *6, *7, *8, *9, *10A, *14, *17, *29, *41
CYP3A5	rs776746, rs10264272, rs41303343	*1, *3, *6, *7
CYP4F2	rs2108622	*1, *3
DPYD	rs3918290, rs56038477, rs67376798, rs115232898, rs55886062	*1, *2A,1236G>A, 2846A>T, 557A->G, *13
NUDT15	rs116855232, rs186364861	*1, *2, *3, *5
SLCO1B1	rs4149056	*1, *5
TPMT‡	rs1800462, rs1800460, rs1142345, rs1800584, rs56161402	*1, *2, *3B, *3C, *4, *8
VKORC1	rs9923231	−1639G>A

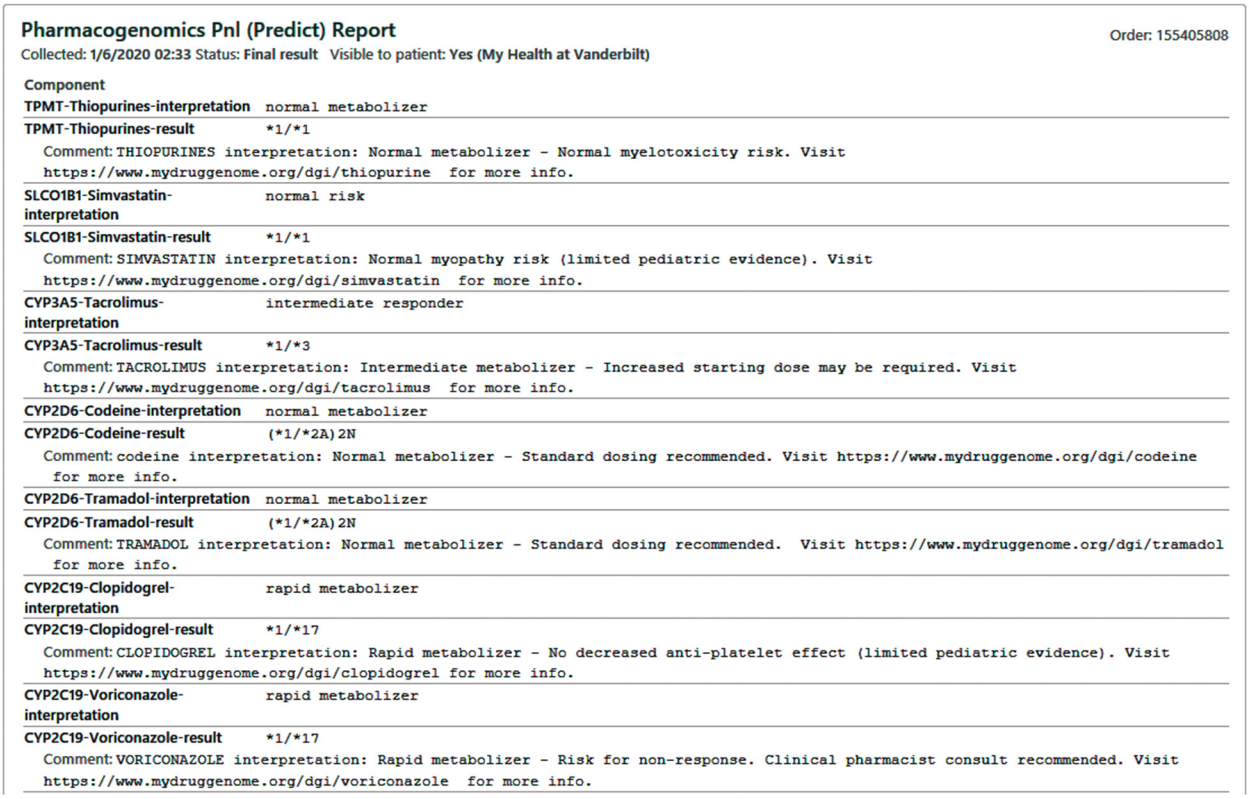
†*CYP2D6* copy number is determined by a separate assay; ‡If variants rs1800460 and rs1142345 are both present, *3A allele is presumed, but cannot rule out *3B/*3C compound heterozygosity.

Table S2. CPIC guidance updates as of June 2020

Drug Gene Interaction	Publication Date	Variants Updates	Guideline Updates	Examples of Variants and/or Recommendation Updated
Ivacaftor and *CFTR*	Mar 2014	3	1	Addition of *CFTR* variants; G1244E, G1349D, G178R, G551S, etc.
Clopidogrel and *CYP2C19*	Sep 2013	0	1	Focused on patients with ACS undergoing PCI, refined recommendations for variant and novel *CYP2C19* alleles beyond *2
Warfarin and *CYP2C9/VKORC1*	Dec 2016	0	2	Incorporated *CYP4F2*, rs12777823 and ancestry into dosing recommendation
Atomoxetine and *CYP2D6*	Feb 2019	0	1	*CYP2D6* genotype to phenotype translation changes
Codeine and *CYP2D6*	Apr 2014	0	2	*CYP2D6* genotype to phenotype translation changes
Ondansetron/Tropisetron and *CYP2D6*	Dec 2016	0	1	*CYP2D6* genotype to phenotype translation changes
Tamoxifen and *CYP2D6*	Jan 2018	0	1	*CYP2D6* genotype to phenotype translation changes
Selective Serotonin Reuptake Inhibitors and *CYP2D6* and *CYP2C19*	Aug 2015	0	1	*CYP2D6* genotype to phenotype translation changes
Tricyclic Antidepressants and *CYP2D6* and *CYP2C19*	Dec 2016	0	2	*CYP2D6* genotype to phenotype translation changes
Fluoropyrimidines and *DPYD*	Oct 2017	3	2	Refined dose reduction recommendation
Rasburicase and *G6PD*	Aug 2014	1	0	New interpretation of *G6PD* A variant as IV/normal function (previously II-IV/Deficient-normal function)
Carbamazepine/Oxcarbazepine and *HLA*	Dec 2017	0	1	Increased scope of the recommendations expanded to include the use of carbamazepine and oxcarbazepine based on *HLA-A**31:01 and *HLA-B**15:02 genotypes, respectively
Simvastatin and *SLCO1B1*	Oct 2014	0	1	Included brief review on *SLCO1B1* genotype and risk of myopathy for other statins
Thiopurines and *TPMT/NUDT15*	Nov 2018	1	2	Additional recommendations for *TPMT* and *NUDT15* indeterminate phenotypes and updated *NUDT15**9 function status from “uncertain function” to “no function”
Atazanavir and *UGT1A1*	Sep 2015	2	0	Additional information on *UGT1A1**80 allele with very high linkage disequilibrium with *28 and *37

ACS=acute coronary syndrome, PCI= percutaneous coronary intervention

Figure S1. PREDICT's Pharmacogenomics interpretation report, which includes results, interpretations, and recommendations. Evidence links are included to provide additional resources for clinical guidance, including primary literature. A separate laboratory report provides the assay methodology, variants tested and any relevant comments that may be unique to the patient from the reviewing molecular-diagnostics professional. Image is copyright of Epic Systems Corporation and used with permission.



Pharmacogenomics Pnl (Predict) Report Order: 155405808

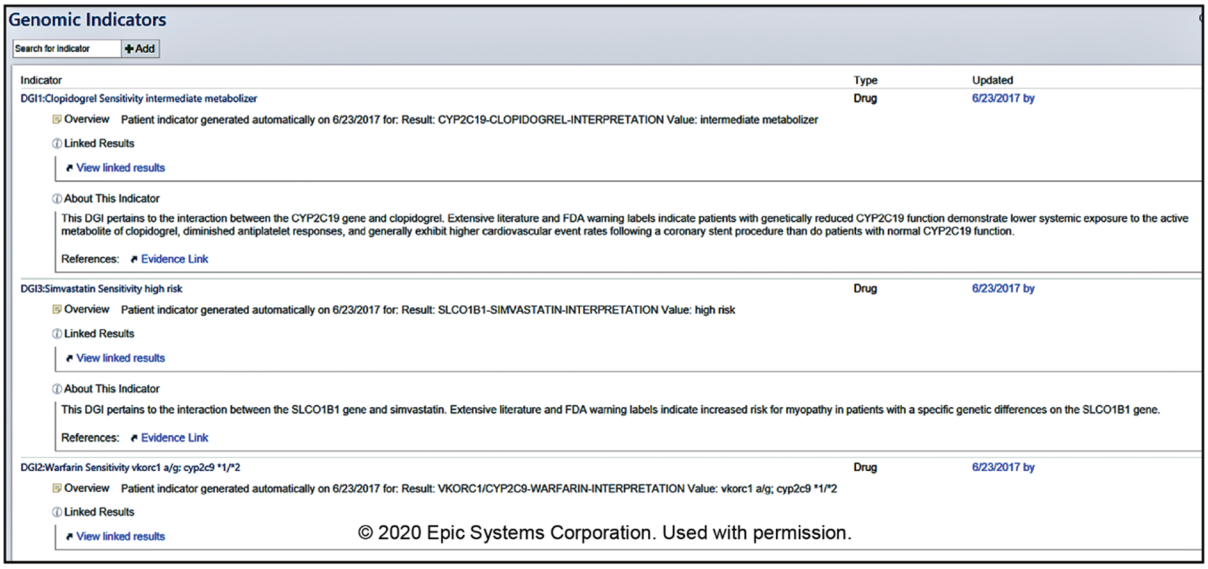
Collected: **1/6/2020 02:33** Status: **Final result** Visible to patient: **Yes (My Health at Vanderbilt)**

Component	
TPMT-Thiopurines-interpretation	normal metabolizer
TPMT-Thiopurines-result	*1/*1
Comment: THIOPURINES interpretation: Normal metabolizer - Normal myelotoxicity risk. Visit https://www.mydruggenome.org/dgi/thiopurine for more info.	
SLCO1B1-Simvastatin-interpretation	normal risk
SLCO1B1-Simvastatin-result	*1/*1
Comment: SIMVASTATIN interpretation: Normal myopathy risk (limited pediatric evidence). Visit https://www.mydruggenome.org/dgi/simvastatin for more info.	
CYP3A5-Tacrolimus-interpretation	intermediate responder
CYP3A5-Tacrolimus-result	*1/*3
Comment: TACROLIMUS interpretation: Intermediate metabolizer - Increased starting dose may be required. Visit https://www.mydruggenome.org/dgi/tacrolimus for more info.	
CYP2D6-Codeine-interpretation	normal metabolizer
CYP2D6-Codeine-result	(*1/*2A)2N
Comment: codeine interpretation: Normal metabolizer - Standard dosing recommended. Visit https://www.mydruggenome.org/dgi/codeine for more info.	
CYP2D6-Tramadol-interpretation	normal metabolizer
CYP2D6-Tramadol-result	(*1/*2A)2N
Comment: TRAMADOL interpretation: Normal metabolizer - Standard dosing recommended. Visit https://www.mydruggenome.org/dgi/tramadol for more info.	
CYP2C19-Clopidogrel-interpretation	rapid metabolizer
CYP2C19-Clopidogrel-result	*1/*17
Comment: CLOPIDOGREL interpretation: Rapid metabolizer - No decreased anti-platelet effect (limited pediatric evidence). Visit https://www.mydruggenome.org/dgi/clopidogrel for more info.	
CYP2C19-Voriconazole-interpretation	rapid metabolizer
CYP2C19-Voriconazole-result	*1/*17
Comment: VORICONAZOLE interpretation: Rapid metabolizer - Risk for non-response. Clinical pharmacist consult recommended. Visit https://www.mydruggenome.org/dgi/voriconazole for more info.	

Figure S2. PREDICT Genomic Indicators before and after system updates. Genomic Indicators are used to deliver PGx results to pharmacists and clinicians within the Epic EHR. A copy of the PREDICT Genomic Indicators from 2018 (a) and 2020 (b) are shown to demonstrate programmatic improvements in the incorporation of clinical support into the EHR. Images are copyright of Epic Systems Corporation and used with permission.

(a)

Genomic Indicators in 2018



(b)

Genomic Indicators in 2020

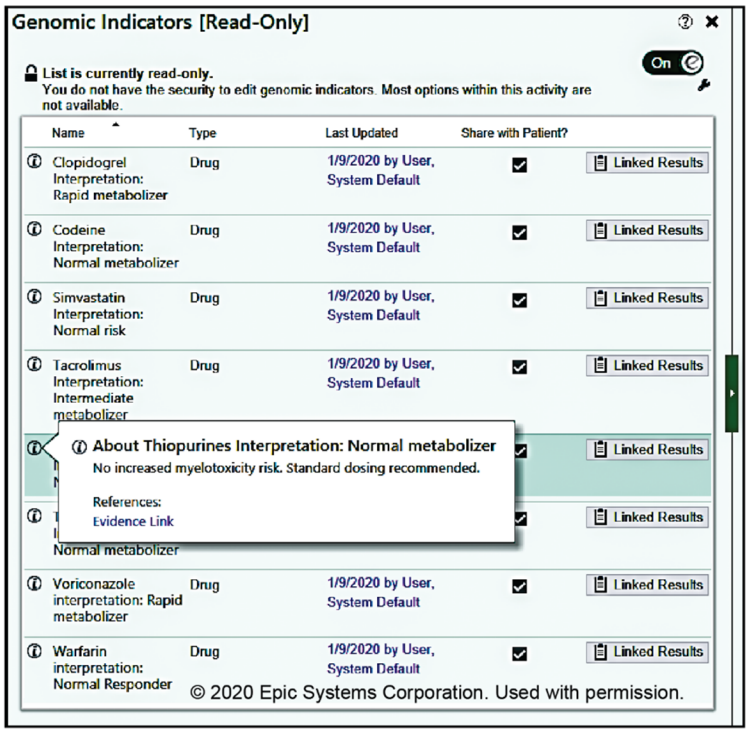
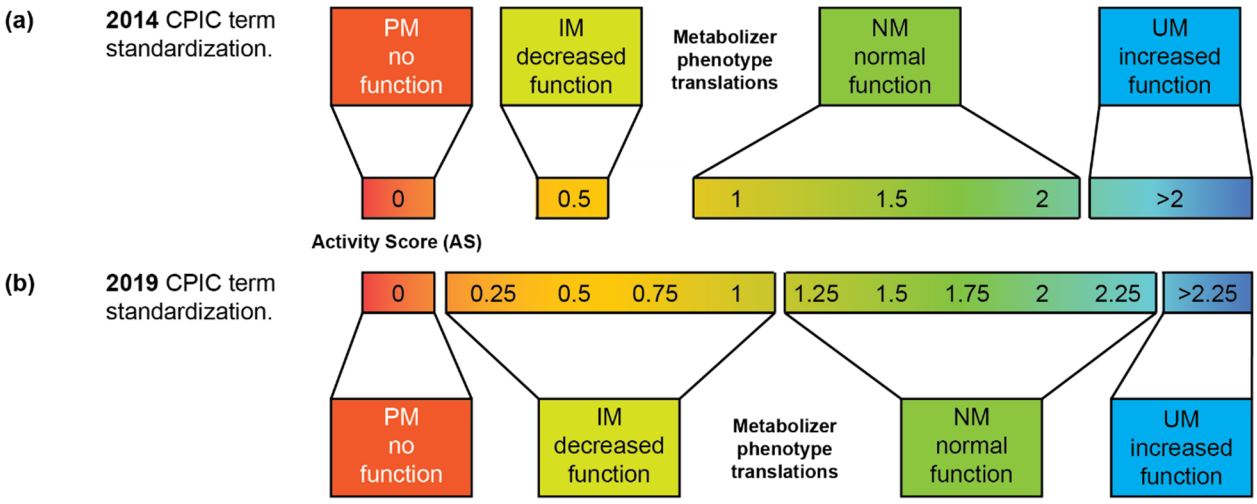


Figure S3. Comparing CYP2D6 genotype-to-phenotype resolution before and after CPIC guidelines.

(a) Previous CPIC genotype-to-phenotype guidance permitted alleles to be scored as 0, 0.5, 1, and 2+ (for gene duplication). The translation of these activity scores meant poor metabolizers (PM) were scored 0, intermediate metabolizers (IM) were 0.5, normal metabolizers (NM) ranged from 1-2, and ultrarapid metabolizers (UM) were scored as >2.

(b) The new CPIC CYP2D6 genotype-to-phenotype guidance now scores alleles as 0, 0.25, 0.5, 1, and 2+. These new activity scores facilitate greater phenotypic resolution wherein PMs were scored 0, IMs range from 0.25-1, NMs range from 1.25-2.25, and UMs are >2.25. Collectively, the revised system captures more genotype-to-phenotype nuance, which is represented by greater activity score coverage in the figure (the activity score spectrum traversing the two panels). Figure adapted from Caudle et al., 2020. [1]



Reference

1. Caudle, K. E. et al. Standardizing CYP2D6 Genotype to Phenotype Translation: Consensus Recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group. Clin Transl Sci 13, 116–124 (2020).