Supplementary Online Content

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eMethods. Projections of Pharmacogenetic Variant Prevalence Among VHA Pharmacy Users and Among New Level A Drug Users

eTable 1. Demographic Characteristics for the Population of Veterans Health Administration Pharmacy Users and Level A Drug Recipients From October 1, 2011 to September 30, 2017

eTable 2. Pharmacogenetic Variant Frequencies for Level A Gene-Drug Associations in Reference Population Groups

eTable 3. Projections for the Prevalence of Actionable Pharmacogenetics Genotypes Among Veterans Health Administration Pharmacy Users

eTable 4. Projected Frequency of Actionable Phenotypes for CYP2C9, CYP2C19, and CYP2D6 Used to Estimate the Proportions of Level A Drug Users With Actionable Phenotypes

eTable 5. Data Used to Estimate the Admixture of European Ancestry Among African American Veterans Used in Sensitivity Analysis

eTable 6. Sensitivity Analysis for the Projected Prevalence of Actionable Genotypes Among Veterans Health Administration Pharmacy Users Obtained Under Different Population Models

eTable 7. Estimation of the Proportion of Veterans Health Administration Pharmacy Users Carrying at Least 1 Pharmacogenetic Variant Allele

eTable 8. Estimation of the Proportions of Level A Drug Users With Actionable Phenotypes Described in Figure 2

eTable 9. Summary of Strong Level A Phenotype-Based Recommendation That the Patient Be Prescribed Alternative or Dose-Adjusted Therapy

eTable 10. Estimation of the Proportions of Level A Drug Users at Risk of Drug Nonefficacy or Adverse Effects Described in Figure 3

eFigure. Result of the Sensitivity Analysis for the Projected Prevalence of Actionable Genotypes Under Different Population Models

eReferences.

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eMethods. Projections of Pharmacogenetic Variant Prevalence Among VHA Pharmacy Users and Among New Level A Drug Users

Estimating the prevalence of actionable PGx variants among VHA Pharmacy users

The prevalence of PGx variants was calculated assuming that the Hardy-Weinberg law applies to the VHA population as a large, randomly mating population with negligible rates of mutation and migration. Under this law, genotype frequencies are expected to follow the frequencies of \( p^2, 2pq \) and \( q^2 \) for \( p \) and \( q \) being the frequencies of two alleles of a bi-allelic gene. For genotypes with more than two alleles, we treated variants in the same gene as mutually exclusive, and the frequency of the wild-type allele was calculated as 1 minus the sum of the actionable variant minor allele frequencies (MAFs) reported for a particular racial/ethnic group (eTable 2). This approach is conservative as it ignores existing variants with lower levels of evidence for an abnormal function.

For the gene \( G6PD \) that is located on the X chromosome, we estimated the frequency of actionable genotypes separately by sex; the frequency of actionable genotypes among male patients (\( X^*Y \)) was estimated as the sum of MAF, and as the frequency of homozygote carriers for female patients (\( X^*X^* \)); we weighted separately the gender frequencies for the two ancestry groups to account for the greater number of women Veterans of African ancestry vs European ancestry (16% vs 8%, respectively) (eTable 3).

Estimations using weighted phenotype frequencies allowed us to account for the frequent combinations of genetic variants at those three loci, and the variations in number of copies for \( CYP2D6 \).\(^1\)

Modeling the population diversity

To account for the diversity of the VHA population we weighted those estimates to produce the number of actionable genotypes among VHA patients with a representation of 15% patients of African ancestry and 85% of patients of European ancestry that are the two predominant groups, and reflected the proportions of VHA Pharmacy users of African ancestry in our sample (eTable 1).\(^2,3\) VHA enrollees with a race/ethnicity that was either unknown or Hispanic, were merged into the European ancestry group.\(^2,3\) Additionally, we performed sensitivity analyses to model the population diversity, accounting for European admixture among African Americans (eTables 5 & 6).

Estimating the proportion of VHA Pharmacy users who would carry at least one actionable variant

We estimated the proportion of Veterans who would carry at least one actionable variant as 1 minus the product of the probabilities of a wildtype genotype at each locus (compiled in eTable 2, as 1 minus the sum of frequencies for the Level-A variant alleles). Probabilities were treated as independent as all genes included in the study are carried by separate chromosomes, except for \( CYP2C9 \) and \( CYP2C19 \) located both on chromosome 10. A sensitivity analysis was performed accounting for the linkage of the variant alleles of \( CYP2C9 \) with the wildtype allele of \( CYP2C19 \) genes which yielded similar estimates.

Identification of patients receiving a new prescription for clopidogrel within 30 days after a percutaneous coronary intervention

In the case of clopidogrel, clinical guidelines are strongest for the impact of PGx testing in the setting of percutaneous coronary intervention (PCI); therefore, we reported the projected number of patients with actionable phenotypes among those patients receiving a new prescription for clopidogrel within 30 days after a PCI, as indicated by the presence of a procedure code [CPT 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, 92980, 92981, C1874-C1877, C9600-C9603].\(^4\) As many Veterans undergoing PCI have the procedure done at a non-VA medical center, we included patients with a procedure code either from the OMOP Procedure Occurrence table for all procedures performed at VA, and from the CDW Fee Basis table for all procedures performed outside VA and paid by VA, which indicates that PCI was performed in the community.

Projecting the clinical impact of Level-A gene-drug interactions

Using the phenotype data, we identified a subgroup of patients with projected phenotypes putting them at high risk of being exposed to a drug for which they have a high likelihood of 1) non-efficacy and/or 2) drug toxicity and adverse events, and characterized the anticipated nature of the toxicities. We limited our analyses to the medications in Figure 1 with a strong CPIC level-A phenotype-based recommendation that the patient be prescribed alternative or dose-adjusted therapy. For the drug warfarin, we accounted for the combinations of alleles between
the two genes assuming independence of genes carried on different chromosomes (CYP2C9 on chromosome 10 and VKORC1 on chromosome 16). These recommendations applied to the following drug-gene interactions: simvastatin-SLC01B1 “intermediate to low function” carriers; codeine-CYP2D6 ultra-rapid and poor metabolizers; clopidogrel-CYP2C19 poor metabolizers; allopurinol-HLA-B*5801 carriers; paroxetine-CYP2D6 ultra-rapid metabolizers. We graphically depicted the absolute number of patients who were exposed to these high-risk medications by their risk of drug non-efficacy and/or toxicity.
**eTable 1.** Demographic Characteristics for the Population of Veterans Health Administration Pharmacy Users And Level A Drug Recipients From October 1, 2011 to September 30, 2017

| Characteristic               | Pharmacy users a | Level-A drug users b | New Level-A drug users c |
|-----------------------------|------------------|----------------------|--------------------------|
| Total, No.                  | 7,769,359        | 4,259,153            | 2,943,872                |
| Age at FY2012, mean (SD), y | 58.1 (17.8)      | 60.2 (16.2)          | 57.1 (16.3)              |
| Sex                         |                  |                      |                          |
| Men                         | 7,021,504 (90.4%)| 3,926,132 (92.2%)    | 2,668,941 (90.7%)        |
| Women                       | 747,564 (9.6%)   | 332,929 (7.8%)       | 274,859 (9.3%)           |
| Not specified               | 291 (<0.1%)      | 92 (<0.1%)           | 72 (<0.1%)               |
| Race/Ethnicity              |                  |                      |                          |
| African American            | 1,195,906 (15.4%)| 703,837 (16.5%)      | 535,992 (18.2%)          |
| White                       | 5,153,274 (66.3%)| 2,929,081 (68.8%)    | 1,984,045 (67.4%)        |
| Hispanic                    | 450,692 (5.8%)   | 251,422 (5.9%)       | 192,328 (6.5%)           |
| Other d                     | 187,000 (2.4%)   | 96,276 (2.3%)        | 71,410 (2.4%)            |
| Unknown                     | 782,487 (10.1%)  | 278,537 (6.5%)       | 160,097 (5.4%)           |

Abbreviations: FY, fiscal year; VHA, Veterans Health Administration

a Unique patients identified in the Veterans Affairs Corporate Data Warehouse based at least one prescription received from VHA Pharmacy in fiscal years 2012-2017

b Patients with at least one prescription for a Level-A drug received from VHA Pharmacy in fiscal years 2012-2017.

c Patients with a new prescription for a Level-A drug received from VHA Pharmacy in fiscal years 2012-2017.

d Other race: Asian, American Indian or Alaskan Native, and Native Hawaiian or Pacific Islander
## eTable 2. Pharmacogenetic Variant Frequencies for Level A Gene-Drug Associations in Reference Population Groups

| Gene      | Allele | Functional status          | Carrier affected | Reference SNP | Population-specific variant frequency^a |
|-----------|--------|-----------------------------|------------------|---------------|----------------------------------------|
|           |        |                             |                  |               | AFR        | EUR        | ASW        | AMR        |
| CYP2C9    | *2     | decreased function          | 1 or 2 copies    | rs1799853     | 0.008      | 0.124      | 0.041      | 0.099      |
| CYP2C9    | *3     | decreased function          | 1 or 2 copies    | rs1057910     | 0.002      | 0.073      | 0.037      | 0.016      |
| CYP2C9    | *5     | possible decreased          | 1 or 2 copies    | rs28371686    | 0.017      | -          | 0.025      | 0.001      |
| CYP2C9    | *6     | no function                 | 1 or 2 copies    | rs9332131     | 0.008      | -          | -          | -          |
| CYP2C9    | *8     | possible decreased          | 1 or 2 copies    | rs7900194     | 0.053      | 0.002      | 0.033      | 0.001      |
| CYP2C9    | *11    | possible decreased          | 1 or 2 copies    | rs28371685    | 0.024      | 0.002      | 0.008      | 0.001      |
| VKORC1    | 1639 G>A| increased warfarin sensitivity | 1 or 2 copies  | rs9923231     | 0.100      | 0.410      | 0.148      | 0.411      |
| CYP2C19   | *2     | No function                 | 2 copies         | rs12767583    | 0.169      | 0.124      | 0.139      | 0.104      |
| CYP2C19   | *3     | No function                 | 2 copies         | rs4986893     | 0.002      | 0.073      | -          | -          |
| CYP2C19   | *4     | No function                 | 2 copies         | rs28399504    | -          | -          | -          | 0.003      |
| CYP2C19   | *8     | No function                 | 2 copies         | rs41291556    | 0.001      | -          | 0.008      | -          |
| CYP2C19   | *17    | Increased function          | 1 or 2 copies    | rs12248560    | 0.235      | 0.224      | 0.197      | 0.120      |
| CYP2D6    | *3     | No function                 | 2 copies         | rs35742686    | 0.002      | 0.019      | 0.016      | 0.006      |
| CYP2D6    | *4     | No function                 | 2 copies         | rs3892097     | 0.061      | 0.186      | 0.123      | 0.130      |
| CYP2D6^6 | *5     | No function                 | 2 copies         | n/a; deletion | 0.061      | 0.028      | 0.064      | 0.021      |
| CYP2D6    | *6     | No function                 | 2 copies         | rs5030655     | 0.001      | 0.020      | 0.008      | 0.003      |
| CYP2D6    | *7     | No function                 | 2 copies         | rs5030867     | -          | 0.000      | -          | -          |
| CYP2D6    | *8     | No function                 | 2 copies         | rs5030865     | -          | 0.000      | -          | -          |
| CYP2D6    | *9     | decreased function          | 2 copies         | rs5030656     | 0.001      | 0.026      | 0.008      | 0.013      |
| CYP2D6    | *10    | decreased function          | 2 copies         | rs1065852     | 0.041      | 0.028      | 0.156      | 0.148      |
| CYP2D6    | *17    | decreased function          | 2 copies         | rs28371706    | 0.218      | 0.020      | 0.148      | 0.009      |
| CYP2D6    | *29    | decreased function          | 2 copies         | rs59421388    | 0.065      | 0.001      | 0.041      | 0.003      |
| CYP2D6    | *41    | decreased function          | 2 copies         | rs28371725    | 0.087      | 0.087      | 0.016      | 0.062      |
| CYP2D6^6  | Gene duplication | Increased function | > 1 copy | n/a | 0.045 | 0.033 | 0.034 | 0.048 |
| CYP3A5^7  | *1     | functional allele           | 1 or 2 copies    | n/a           | 0.560      | 0.078      | 0.605      | 0.202      |
| Gene     | Allele | Functional status | Carrier affected<sup>b</sup> | Reference SNP | AFR  | EUR  | ASW  | AMR  |
|----------|--------|------------------|------------------|----------------|------|------|------|------|
| SLC10A1  | *5     | decreased function | 1 or 2 copies    | rs4149056      | 0.014| 0.161| 0.066| 0.134|
| UGT1A1   | *80    | decreased function | 2 copies         | rs887829       | 0.493| 0.298| 0.459| 0.379|
| TPMT     | *2     | No function       | 1 or 2 copies    | rs1800462      | 0.001| 0.006| 0.008| 0.006|
| TPMT     | *3     | No function       | 1 or 2 copies    | rs1800460      | 0.003| 0.028| 0.025| 0.040|
| DPYD     | *2A    | No function       | 1 or 2 copies    | rs3918290      | 0.001| 0.005| 0.008| 0.001|
| DPYD     | D949V  | decreased function | 1 or 2 copies    | rs67376798     | 0.001| 0.007| 0.008| 0.003|
| G6PD<sup>c</sup> | A-[202A;376G] | deficient | Male: 1 copy; female 2 copies | rs1050828, rs1050829 | 0.134| -    | 0.167| 0.013|
| G6PD<sup>c</sup> | Asahi [202A;376A] | deficient | Male: 1 copy; female 2 copies | rs1050828 | 0.001| -    | -    | -    |
| G6PD<sup>c</sup> | A [202G;376G] | deficient | Male: 1 copy; female 2 copies | rs1050829 | 0.204| 0.004| 0.125| 0.015|
| IFNL3B   | r151-2G>A | decreased response | 1 or 2 copies    | rs12979860     | 0.390| 0.630| 0.320| 0.601|
| HLA-A<sup>a</sup> | *31:01 | hypersensitivity reaction | 1 or 2 copies    | n/a            | 0.005| 0.028| 0.010| 0.064|
| HLA-B<sup>a</sup> | *57:01 | hypersensitivity reaction | 1 or 2 copies    | n/a            | 0.008| 0.032| 0.001| 0.016|
| HLA-B<sup>a</sup> | *58:01 | severe cutaneous adverse reactions | 1 or 2 copies    | n/a            | 0.054| 0.013| 0.039| 0.011|
| HLA-B<sup>a</sup> | *15:02 | Stevens-Johnson syndrome, toxic epidermal necrolysis | 1 or 2 copies    | n/a            | 0.0001| 0.0004| 0.001| 0.0004|

Abbreviation: AFR: African ancestry; AMR: Americas; ASW, People with African Ancestry in Southwest USA; EUR, European ancestry; SNP, single nucleotide polymorphism.

<sup>a</sup> Variant frequency reported as the minor allele frequency for the three populations AFR, EUR and AMER, and the ASW group in the 1000 Genomes Project Phase 3<sup>9</sup>, else otherwise indicated by a citation. SNP are specific for a gene variant, except in the case of G6PD deficient alleles characterized by the combination of two SNPs. Variants of a same gene are considered mutually exclusive.

<sup>b</sup> Specifies if carriers affected by the gene-drug association are either homozygous (i.e., 2 copies), or include both homozygous and heterozygous carriers (i.e., 1 or 2 copies).

<sup>c</sup> Frequencies of G6PD deficient alleles in the table take in account the linkage disequilibrium observed between rs1050828 and rs1050829 (estimated using LD pair).<sup>10</sup>

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### eTable 3. Projections for the Prevalence of Actionable Pharmacogenetics Genotypes Among Veterans Health Administration Pharmacy Users

| Gene   | AFR subpopulation | EUR subpopulation | VHA pop |
|--------|-------------------|-------------------|---------|
|        | Alleles, grouped by function | Allele freq. | Heterozygote freq. [2*p*wt] | Compound heterozygote freq. [2*p*r] | Homozygote freq. [p*p] | Actionable GT | Allele freq. | Heterozygote freq. [2*p*wt] | Compound heterozygote freq. [2*p*r] | Homozygote freq. [p*p] | Actionable GT | Actionable GT |
|        |                   |                   |         |                        |                        |                     |                   |                        |                        |                     |                     |              |              |
| **CYP 2C9** |                  |                   |         |                        |                        |                     |                   |                        |                        |                     |                     |              |              |
| wt (other than *2-*11) | 0.888 | 0.014 | 0.002 | <0.001 | 0.124 | 0.198 | 0.019 | 0.015 | 0.799 | 0.124 | 0.198 | 0.019 | 0.015 |
| *2  | 0.008 | 0.014 | 0.002 | <0.001 | 0.124 | 0.198 | 0.019 | 0.015 |          |          |          |          |          |
| *3  | 0.002 | 0.004 | <0.001 | <0.001 | 0.073 | 0.117 | 0.001 | 0.005 |          |          |          |          |          |
| *5  | 0.017 | 0.030 | 0.003 | <0.001 | -     | <0.001 | -     | -     |          |          |          |          |          |
| *6  | 0.008 | 0.014 | 0.001 | <0.001 | -     | <0.001 | -     | -     |          |          |          |          |          |
| *8  | 0.053 | 0.094 | 0.003 | 0.003 | 0.002 | 0.003 | <0.001 | <0.001 |          |          |          |          |          |
| *11 | 0.024 | 0.043 | 0.001 | 0.003 | 0.002 | 0.003 | <0.001 | <0.001 |          |          |          |          |          |
| Decreased function (1 or 2 copies) | 0.199 | 0.009 | 0.004 | 21.1% | 0.321 | 0.020 | 0.021 | 36.2% | 33.9% |

| **VKORC1** |                  |                   |         |                        |                        |                     |                   |                        |                        |                     |                     |              |              |
| wildtype | 0.900 |          |         |                        |                        |                     |                   |                        |                        |                     |                     |              |              |
| (-1639 G>A) | 0.100 | 0.180 | n/a    | 0.010 | 0.41 | 0.484 | n/a | 0.168 |          |          |          |          |          |

| Increased sensitivity (1 or 2 copies) | 0.180 | n/a | 0.010 | 19.0% | 0.484 | n/a | 0.168 | 65.2% | 58.3% |

| **CYP 2C19** |                  |                   |         |                        |                        |                     |                   |                        |                        |                     |                     |              |              |
| wildtype (other than *2-*17) | 0.593 |          |         |                        |                        |                     |                   |                        |                        |                     |                     |              |              |
| *2  | 0.169 | 0.200 | 0.001 | 0.029 | 0.124 | 0.144 | 0.018 | 0.015 |          |          |          |          |          |
| *3  | 0.002 | 0.002 | <0.001 | <0.001 | 0.073 | 0.085 | -     | -     |          |          |          |          |          |
| *4  | -     | -     | -     | -     | -     | -     | -     | -     |          |          |          |          |          |
| *8  | 0.001 | 0.001 | <0.001 | -     | -     | -     | -     | -     |          |          |          |          |          |
| Decreased function (2 copies) | 0.204 | 0.001 | 0.029 | 23.4% | 0.228 | 0.018 | 0.021 | 26.7% | 26.2% |
| *17 | 0.235 | 0.279 | 0.114 | 0.055 | 0.224 | 0.260 | 0.118 | 0.050 |          |          |          |          |          |
| Increased function (1 or 2 copies) | 0.279 | 0.114 | 0.055 | 44.8% | 0.260 | 0.118 | 0.050 | 42.8% | 43.1% |

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| Gene | AFR subpopulation | EUR subpopulation | VHA pop |
|------|-------------------|-------------------|---------|
|      | Alleles, grouped by function | Allele freq. | Heterozygote freq. \([2^*p^*wt]\) | Compound heterozygote freq. \([2^*p^*r]\) | Homozygote freq. \([p^*p]\) | Actionable GT | Allele freq. | Heterozygote freq. \([2^*p^*wt]\) | Compound heterozygote freq. \([2^*p^*r]\) | Homozygote freq. \([p^*p]\) | Actionable GT | Actionable GT |
|      |                   |                   |               |               |               |               |                   |               |               |               |               |               |               |
| CYP 2D6 | wildtype (all other than *3-*41 or duplicate) | 0.463 | 0.002 | 0.002 | <0.001 | 0.019 | 0.022 | 0.015 | <0.001 | 0.585 | 0.019 | 0.022 | 0.015 | <0.001 |
|      | *3 | 0.002 | 0.002 | 0.002 | <0.001 | 0.019 | 0.022 | 0.015 | <0.001 | 0.585 | 0.019 | 0.022 | 0.015 | <0.001 |
|      | *4 | 0.061 | 0.056 | 0.058 | 0.004 | 0.186 | 0.218 | 0.078 | 0.035 | 0.019 | 0.022 | 0.015 | <0.001 |
|      | *5 | 0.061 | 0.056 | 0.050 | 0.004 | 0.028 | 0.033 | 0.010 | <0.001 | 0.019 | 0.022 | 0.015 | <0.001 |
|      | *6 | 0.001 | 0.001 | <0.001 | <0.001 | 0.020 | 0.023 | 0.006 | <0.001 | 0.019 | 0.022 | 0.015 | <0.001 |
|      | *7 | - | - | - | - | - | - | - | - | - | - | - | - | - |
|      | *8 | - | - | - | - | - | - | - | - | - | - | - | - | - |
|      | *9 | 0.001 | 0.001 | <0.001 | <0.001 | 0.026 | 0.030 | 0.007 | <0.001 | 0.019 | 0.022 | 0.015 | <0.001 |
|      | *10 | 0.041 | 0.038 | 0.030 | 0.002 | 0.028 | 0.033 | 0.006 | <0.001 | 0.019 | 0.022 | 0.015 | <0.001 |
|      | *17 | 0.218 | 0.202 | 0.066 | 0.048 | 0.020 | 0.023 | 0.003 | <0.001 | 0.019 | 0.022 | 0.015 | <0.001 |
|      | *29 | 0.065 | 0.060 | 0.011 | 0.004 | 0.001 | 0.001 | <0.001 | <0.001 | 0.019 | 0.022 | 0.015 | <0.001 |
|      | *41 | 0.087 | 0.081 | 0.087 | 0.102 | 0.087 | 0.102 | 0.087 | 0.102 | 0.019 | 0.022 | 0.015 | <0.001 |
|      | Decreased function (2 copies) | n/a | n/a | 0.061 | 6.1% | n/a | n/a | 0.038 | 3.8% | 4.1% | n/a | n/a | 0.038 | 3.8% | 4.1% |
|      | Increased function (frequency of phenotype) | n/a | n/a | 0.061 | 6.1% | n/a | n/a | 0.038 | 3.8% | 4.1% | n/a | n/a | 0.038 | 3.8% | 4.1% |
|      | Total actionable for CYP2D6 | 10.5% | 10.5% | 10.5% | 10.5% | 10.5% | 10.5% | 10.5% | 10.5% | 10.5% | 10.5% | 10.5% | 10.5% | 10.5% | 10.5% |

CYP 3A5

|      | alleles other than *1 | 0.440 | 0.922 |
|      | *1 | 0.560 | 0.493 | 0.314 | 0.078 | 0.144 | 0.006 | 15.0% | 24.8% |
|      | Extensive metabolizer (1 or 2 copies) | 0.493 | 0.314 | 80.6% | 0.144 | 0.006 | 15.0% | 24.8% |
| Gene   | AFR subpopulation | EUR subpopulation | VHA pop |
|--------|-------------------|-------------------|---------|
|        | Alleles, grouped by function | Allele freq. | Heterozygote freq. [2*p*wt] | Compound heterozygote freq. [2*p*r] | Homozygote freq. [p*p] | Actionable GT | Allele freq. | Heterozygote freq. [2*p*wt] | Compound heterozygote freq. [2*p*r] | Homozygote freq. [p*p] | Actionable GT | Actionable GT |
|        | SLCO1B1 wildtype (other than *5) | 0.986 | 0.014 | 0.014 | 0.028 | <0.001 | 0.161 | 0.270 | 0.0260 | 0.0260 | 29.6% | 25.6% |
|        | Intermediate to low function (1 or 2 copies) | 0.028 | <0.001 | 2.8% | 0.270 | 0.0260 | 29.6% | 25.6% |
|        | UGT1A1 wildtype (other than *80) | 0.507 | 0.028 | 0.028 | 0.243 | <0.001 | 0.298 | 0.418 | 0.089 | 0.089 | 8.9% | 11.2% |
|        | Deficiency (2 copies) | n/a | 0.243 | 24.3% | n/a | 0.089 | 8.9% | 11.2% |
|        | TPMT wildtype (other than *2, *3) | 0.996 | 0.001 | 0.001 | 0.006 | <0.001 | 0.006 | 0.12 | <0.001 | <0.001 | 0.006 | 0.12 | <0.001 | <0.001 |
|        | *2 | 0.001 | 0.002 | <0.001 | <0.001 | 0.006 | 0.12 | <0.001 | <0.001 | 0.006 | 0.12 | <0.001 | <0.001 |
|        | *3 | 0.003 | 0.006 | <0.001 | <0.001 | 0.028 | 0.054 | <0.001 | <0.001 | 0.028 | 0.054 | <0.001 | <0.001 |
|        | Deficiency (1 or 2 copies) | 0.008 | <0.001 | <0.001 | 0.8% | 0.066 | <0.001 | <0.001 | 0.67% | 5.8% |
|        | DPYD wildtype (other than *2A, D949V) | 0.998 | 0.001 | 0.001 | 0.005 | <0.001 | 0.005 | 0.10 | <0.001 | <0.001 | 0.005 | 0.10 | <0.001 | <0.001 |
|        | *2A | 0.001 | 0.002 | <0.001 | <0.001 | 0.005 | 0.10 | <0.001 | <0.001 | 0.005 | 0.10 | <0.001 | <0.001 |
|        | D949V | 0.001 | <0.001 | <0.001 | 0.007 | <0.001 | 0.007 | <0.001 | <0.001 | 0.007 | <0.001 | <0.001 | <0.001 |
|        | Deficiency (1 or 2 copies) | 0.002 | <0.001 | <0.001 | 0.2% | <0.001 | <0.001 | <0.001 | 1.0% | 0.9% |
|        | G6PD wildtype [202G;376A] | 0.661 | 0.001 | 0.001 | 0.001 | <0.001 | 0.001 | 0.001 | <0.001 | <0.001 | 0.001 | 0.001 | <0.001 | <0.001 |
|        | A- [202A;376G] | 0.134 | 0.001 | 0.001 | 0.001 | <0.001 | 0.001 | 0.001 | <0.001 | <0.001 | 0.001 | 0.001 | <0.001 | <0.001 |

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| Gene | Alleles, grouped by function | AFR subpopulation | EUR subpopulation | VHA pop |
|------|-----------------------------|------------------|------------------|---------|
|      |                             | Allele freq. | Heterozygote freq. | Compound heterozygote freq. | Actionable GT | Allele freq. | Heterozygote freq. | Compound heterozygote freq. | Actionable GT |
|      |                             | [2*p*wt]     | [2*p*r]          | [p*p]       |                | [2*p*wt]     | [2*p*r]          | [p*p]       |                |
| G6PD | A [202G;376G] | 0.204         | 0.004            |             |                | 0.339         | 0.004            |             |                |
|      | Deficiency - all            | 0.339         | 0.004            |             |                | 0.004         | 0.004            |             |                |
|      | Male (XY)                   | 0.339         | n/a              | 0.004       | n/a            | 0.115         | n/a              | <0.001      | 0.4%          | 4.9%          |
|      | Female (XX)                 | n/a           | 0.018            | 30.3%       | 0.004          | n/a           | <0.001           | 0.4%        | 82.8%         |
|      | weighted for gender         | 0.284         | 0.018            | 30.3%       | 0.004          | 0.115         | 0.004            |             |                |
| IFNL3| other than r151-2G>A         | 0.610         | 0.370            |             |                | 0.476         | 0.152            | 62.8%       | 0.466         | 0.400         |
|      | r151-2G>A                   | 0.390         | 0.476            | 0.152       | 0.630          | 0.466         | 0.400            |             |                |
|      | Unfavorable response        | 0.476         | 0.152            | 62.8%       | 0.466          | 0.400         | 86.3%            | 82.8%       |                |
| HLA  | Presence (1 or 2 copies)    |                |                  |             |                | 0.001         | 0.001            | 5.5%        | 4.8%          |
|      | HLA-A *31:01                | 0.005         | 0.010            | <0.001      | 1.0%           | 0.028         | 0.054            | 0.001       | 5.5%          | 4.8%          |
|      | HLA-B *57:01                | 0.008         | 0.016            | <0.001      | 1.6%           | 0.032         | 0.062            | 0.001       | 6.3%          | 5.6%          |
|      | HLA-B *58:01                | 0.054         | 0.102            | 0.003       | 10.5%          | 0.013         | 0.026            | <0.001      | 2.6%          | 3.8%          |
|      | HLA-B *15:02                | 0.0001        | <0.001           | <0.001      | 0.0%           | <0.001        | 0.001            | <0.001      | 0.1%          | 0.1%          |

Abbreviation: Freq.: frequency; GT: genotype; pop: population

Population-specific prevalence of actionable genotypes were weighted to generate population estimates using the weights of 15% for AFR and 85% for EUR (Model 1 in eTable 5).

We assume that the variants were mutually exclusive, and the frequency of wildtype alleles is obtained as 1 minus the sum of frequencies of the variant alleles.

The frequency of homozygote genotypes is calculated as the square of the frequency of the variant (1 copy on each chromosome), and the frequency of heterozygote is estimated as 2 times the product of the variant allele by the other allele. The frequencies of compound heterozygotes combining two variant alleles were calculated in series to avoid double-counting of combinations, e.g. allele A was combined to alleles B to E, then allele B is combined to allele C to E, allele C is combined to allele D to E, and so on.

*In the case of CYP3A5, the actionable allele is the reference allele *1 that encodes functional CYP3A5 and for which dose adjustment is recommended; other alleles are nonfunctional.*

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### eTable 4. Projected Frequency of Actionable Phenotypes for *CYP2C9, CYP2C19,* and *CYP2D6* Used to Estimate the Proportions of Level A Drug Users With Actionable Phenotypes

| Gene       | Phenotype                      | Prevalence for AFR | Prevalence for EUR | Projected for VHA population |
|------------|--------------------------------|--------------------|--------------------|------------------------------|
| *CYP2C9*¹⁷ | Normal metabolizer             | 75.2%              | 64.0%              | 65.7%                        |
|            | Intermediate metabolizer       | 23.1%              | 32.0%              | 30.7%                        |
|            | Poor metabolizer               | 1.8%               | 4.0%               | 3.7%                         |
| *CYP2C19*¹² | Ultrarapid Metabolizer         | 2.3%               | 4.6%               | 4.3%                         |
|            | Rapid Metabolizer              | 13.6%              | 26.9%              | 24.9%                        |
|            | Normal Metabolizer             | 16.8%              | 39.2%              | 35.8%                        |
|            | Intermediate Metabolizer       | 24.1%              | 26.8%              | 26.4%                        |
|            | Poor Metabolizer               | 4.8%               | 2.5%               | 2.9%                         |
|            | *Unknown*                      | 38.4%              | 0.0%               | 5.8%                         |
| *CYP2D6*⁶  | Ultrarapid Metabolizer         | 4.5%               | 3.3%               | 3.4%                         |
|            | Normal Metabolizer             | 71.9%              | 74.9%              | 74.5%                        |
|            | Normal Metabolizer, Ultrarapid Metabolizer | 0.8% | 1.1% | 1.1% |
|            | Intermediate Metabolizer       | 12.6%              | 7.2%               | 8.0%                         |
|            | Poor Metabolizer               | 1.9%               | 6.1%               | 5.4%                         |
|            | *Unknown*                      | 8.4%               | 7.4%               | 7.5%                         |

Abbreviations: AFR: African ancestry; EUR, European ancestry
**eTable 5. Data Used to Estimate the Admixture of European Ancestry Among African American Veterans Used in Sensitivity Analysis**

| References      | Methods                | Genotyped population (Study)          | Sample size | EUR ancestry |
|-----------------|------------------------|----------------------------------------|-------------|--------------|
| Parra 1998¹³    | PCR on 9 loci          | 10 US sites                            | 1020        | 16.4%        |
| Reiner 2005¹⁴   | 22 SNPs                | 3 US sites (CHS study)                 | 810         | 20.1%        |
| Yaeger 2008¹⁵   | 107 SNPs               | New York region                        | 50          | 14.7%        |
| Allison 2010¹⁶  | 97 SNPs                | 6 US regions (MESA study)              | 712         | 20.2%        |
| Murray 2010¹⁷   | 416 SNPs               | Baltimore/DC (GRAAD study)             | 906         | 19.7%        |
| Bryc 2015¹⁸     | >500,000 SNPs          | US national (23andMe)                 | 1970        | 24.0%        |
| Banda 2015¹⁹    | 250,000 SNPs           | Northern California (Kaiser)           | 3365        | 26.0%        |
| Baharian 2016²⁰ | >500,000 SNPs          | South West (SCCS)                      | 2128        | 14.0%        |
| Baharian 2016²⁰ | >500,000 SNPs          | National (HRS National)                | 1501        | 16.7%        |
| Baharian 2016²⁰ | >500,000 SNPs          | South West (ASW 1000G)                 | 97          | 21.3%        |
| Mathias 2016²¹  | >500,000 SNPs          | 8 US sites                             | 328         | 18.8%        |
| **Weighted average** |                     |                                        | **12887**   | **20.5%**    |

Abbreviations: ASW, People with African Ancestry in Southwest USA; CHS, Cardiovascular Health Study; EUR, European ancestry; GRAAD, Genomic Research on Asthma in the African Diaspora; HRS, Health and Retirement Study; MESA, Multi-Ethnic Study of Atherosclerosis; PCR, polymerase chain reaction; SCCS, Southern Community Cohort Study; SNP, single nucleotide polymorphism;

Number of ancestry markers analyzed, the number of sites and geographic distribution of the genotyped population, contribution of European ancestry among African American participants, and average value weighted for the sample sizes.

Values reported are specific for African American participants in each study.

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**eTable 6. Sensitivity Analysis for the Projected Prevalence of Actionable Genotypes Among Veterans Health Administration Pharmacy Users Obtained Under Different Population Models**

| Gene     | Model 1 AFR 15% | Model 2 AFR 20% | Model 3 AFR 15% 21% EUR admix | Model 4 AFR 20% 21% EUR admix | Model 5 ASW 15% | Model 6 AFR 15% AMR 7% | Average value with 95% CI |
|----------|-----------------|-----------------|-------------------------------|-------------------------------|-----------------|------------------------|---------------------------|
| CYP2C9   | 33.9%           | 33.2%           | 33.3%                         | 32.4%                         | 34.7%           | 32.9%                  | 33.4% ± 0.6%              |
| VKORC1   | 58.3%           | 56.0%           | 58.2%                         | 55.9%                         | 59.5%           | 58.3%                  | 57.7% ± 1.1%              |
| CYP2C19 Decreased function | 26.2%           | 26.0%           | 25.4%                         | 24.9%                         | 25.9%           | 25.6%                  | 25.7% ± 0.3%              |
| CYP2C19 Increased function | 43.1%           | 43.2%           | 41.8%                         | 41.5%                         | 42.3%           | 41.9%                  | 42.3% ± 0.5%              |
| CYP2D6 Decreased function | 4.1%            | 4.3%            | 3.8%                          | 3.8%                          | 4.2%            | 4.2%                   | 4.1% ± 0.1%               |
| CYP2D6 Increased function | 3.4%            | 3.5%            | 3.2%                          | 3.2%                          | 3.3%            | 3.6%                   | 3.4% ± 0.1%               |
| CYP3A5   | 24.8%           | 28.1%           | 21.0%                         | 23.0%                         | 25.4%           | 26.3%                  | 24.8% ± 1.8%              |
| SLC01B1  | 25.6%           | 24.2%           | 25.7%                         | 24.3%                         | 27.1%           | 25.3%                  | 25.4% ± 0.8%              |
| UGT1A1   | 11.2%           | 12.0%           | 10.0%                         | 10.4%                         | 10.7%           | 11.6%                  | 11.0% ± 0.5%              |
| TPMT     | 5.8%            | 5.5%            | 5.8%                          | 5.5%                          | 6.7%            | 6.0%                   | 5.9% ± 0.3%               |
| DPYD     | 0.9%            | 0.8%            | 0.9%                          | 0.8%                          | 1.1%            | 0.8%                   | 0.9% ± 0.1%               |
| G6PD     | 4.9%            | 6.4%            | 3.2%                          | 4.1%                          | 4.2%            | 5.0%                   | 4.6% ± 0.8%               |
| IFNL3    | 82.8%           | 81.6%           | 82.5%                         | 81.2%                         | 81.4%           | 82.6%                  | 82.0% ± 0.5%              |
| HLA-A*31:01 | 4.8%           | 4.6%            | 4.8%                          | 4.6%                          | 5.0%            | 5.3%                   | 4.9% ± 0.2%               |
| HLA-B*57:01 | 5.6%            | 5.4%            | 5.5%                          | 5.3%                          | 5.4%            | 5.4%                   | 5.4% ± 0.1%               |
| HLA-B*58:01 | 3.8%            | 4.2%            | 3.2%                          | 3.4%                          | 3.3%            | 3.7%                   | 3.6% ± 0.3%               |
| HLA-B*15:02 | 0.1%            | 0.1%            | 0.1%                          | 0.1%                          | 0.1%            | 0.1%                   | 0.1% ± 0.0%               |

Abbreviations: AFR: African ancestry; AMR: Americas; ASW, People with African Ancestry in Southwest USA; EUR, European ancestry

Model 1 used in the primary analysis accounting for a mix of 15% patients of African ancestry and 85% of patients of European ancestry. Model 2, alternative weights for 20% patients of African ancestry and 80% of patients of European ancestry. Models 3 and 4 models the admixture of African American patients with a 21% contribution of European ancestry; the
21% contribution was estimated based on the literature review summarized in eTable4. Model 5 applies the variant frequencies for the African American in Southwest USA in the 1000 genome project with weights of 15% ASW/85% EUR. Model 6 tests the effect of accounting the contribution of populations from American origin, and models the population as 15% for AFR, 7% AMR (population from Americas), and 78% EUR.

PGx variants values for each population are listed in eTable 2; all calculations follow the same model as applied to Model 1 in eTable 1. Average values for the six models with the range of 95% CI interval are presented in the right-hand column.

For gender adjustment in G6PD estimation, we applied proportions of women patients for each population as reported in the 2017: AFR and ASW, 16% women patients; AMR, 11%; and EUR, 8%.
eTable 7. Estimation of the Proportion of Veterans Health Administration Pharmacy Users Carrying at Least 1 Pharmacogenetic Variant Allele

| Gene     | Genotypes with wildtype phenotype | Prevalence for AFR | Prevalence for EUR |
|----------|-----------------------------------|-------------------|--------------------|
| CYP2C9   | wt/wt                             | 0.789             | 0.638              |
| VKORC1   | wt/wt                             | 0.810             | 0.348              |
| CYP2C19  | total                             | 0.556             | 0.563              |
|          | wt/wt                             | 0.352             | 0.335              |
|          | wt/var with decreased function     | 0.204             | 0.228              |
| CYP2D6   | total                             | 0.712             | 0.828              |
|          | wt/wt                             | 0.214             | 0.342              |
|          | wt/var with decreased function     | 0.497             | 0.486              |
| CYP3A5   | (other than *1)/(other than *1)   | 0.194             | 0.850              |
| SLCO1B1  | wt/wt                             | 0.972             | 0.704              |
|          | total                             | 0.757             | 0.911              |
|          | wt/wt                             | 0.257             | 0.493              |
|          | wt/*80                            | 0.500             | 0.418              |
| TPMT     | wt/wt                             | 0.992             | 0.933              |
| DPYD     | wt/wt                             | 0.996             | 0.976              |
| G6PD     | 1 wt copy (male)                  | 0.661             | 0.911              |
| IFNL3    | wt/wt                             | 0.372             | 0.137              |
| HLA-A    | wt/wt                             | 0.990             | 0.945              |
| HLA-B    | wt/wt                             | 0.938             | 0.955              |
| Product of all probabilities per group |                   | 0.008             | 0.006              |
| Weighted probability of all wildtype | P                  | 0.006             |                   |
| Probability of at least one actionable variant | 1 - P       | 0.994             |                   |

Abbreviations: AFR: African ancestry; EUR, European ancestry; wt, wildtype

The probability of having at least one actionable variant was calculated as 1 minus the probability of a wildtype phenotype at each of the loci analyzed, which is the product of the probabilities of a wildtype phenotype for each gene. For CYP2C19, CYP2D6 and SLCO1B1, a wildtype phenotype can result from carrying 1 or 2 copies of the wildtype allele, and the probability of a wildtype phenotype is the sum of the probabilities of the two genotypes that are mutually exclusive.

For CYP3A5, *1 is the actionable allele, and combinations of other alleles results in a non-actionable phenotype.

The model assumes that the genes are independent from each other as they are carried by different chromosomes, except for CYP2C9 and CYP2C19 that are both on chromosome 10. We performed a sensitivity analysis to test the impact of linkage disequilibrium between CYP2C9 and CYP2C19 that results in a complete linkage of CYP2C9 wildtype allele with CYP2C19 variant alleles. The frequency of double allele CYP2C9wt;CYP2C19wt is then the frequency of CYP2C9wt minus the frequency of CYP2C9wt;CYP2C19var (i.e., the frequency of CYP2C19 variant because of complete linkage). After adjustment for linkage disequilibrium, the results were unchanged: the prevalence of CYP2C9wt alleles were 0.481 for AFR and 0.378 for EUR, and the frequencies of a wildtype phenotype for CYP2C9 were 0.231 and 0.142. The final result in the table above was 0.995.

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As warfarin was associated to a high percentage of actionable variants but the number of warfarin prescriptions are on the decline, we performed an additional sensitivity analysis without including the genes associated to warfarin, CYP2C9 and VKORC1. The product of the probabilities of a wildtype phenotype for the ten other genes listed in the table resulted in a decrease of the probability of carrying at least one actionable variant from 0.994 to 0.976.
**eTable 8.** Estimation of the Proportions of Level A Drug Users With Actionable Phenotypes Described in Figure 2

| Drug                  | Unique new users (No.) | Associated genes         | Total prevalence | Projected number of users (No.) |
|----------------------|------------------------|--------------------------|------------------|---------------------------------|
| Tramadol             | 923,671                | CYP2D6<sup>b</sup>       | 8.9%             | 82,092                          |
| Ondansetron          | 604,226                | CYP2D6<sup>c</sup>       | 3.5%             | 20,816                          |
| Simvastatin          | 533,928                | SLCO1B1<sup>a</sup>      | 25.6%            | 136,599                         |
| Simvastatin users prescribed 80 mg initial dose | 125,119 | SLCO1B1<sup>a</sup>      | 25.6%            | 32,010                          |
| Codeine              | 528,159                | CYP2D6<sup>b</sup>       | 8.9%             | 46,941                          |
| Clopidogrel          | 338,295                | CYP2C19<sup>f</sup>      | 29.2%            | 98,900                          |
| Clopidogrel PCI patients<sup>e</sup> | 51,094 | CYP2C19<sup>f</sup>      | 29.2%            | 14,937                          |
| Citalopram           | 266,952                | CYP2C19<sup>d</sup>      | 7.2%             | 19,100                          |
| Allopurinol          | 215,055                | HLA-B:58*01              | 3.8%             | 8,172                           |
| Warfarin             | 205,177                | VKORC1, CYP2C9<sup>g</sup> | 72.6%            | 148,928                         |
| Amitriptyline        | 174,693                | CYP2C19, CYP2D6<sup>h</sup> | 40.8%            | 71,216                          |
| Escitalopram         | 170,690                | CYP2D6<sup>b</sup>       | 8.9%             | 15,170                          |

Abbreviation: PCI, percutaneous coronary intervention

- ^a^ intermediate to low function
- ^b^ ultra-rapid metabolizers and poor metabolizers
- ^c^ ultra-rapid metabolizers only
- ^d^ ultra-rapid metabolizers, and poor metabolizers
- ^e^ new users of clopidogrel receiving the drug within 30 days after a percutaneous coronary intervention
- ^f^ intermediates and poor metabolizers
- ^g^ poor/intermediate metabolizer for CYP2C9 and/or increased sensitivity linked to VKORC1, calculated as the frequency of CYP2C9 poor/intermediate metabolizer;VKORC1 sensitive, plus CYP2C9 poor/intermediate metabolizer;VKORC1 wildtype plus CYP2C9 wildtype;VKORC1 sensitive
- ^h^ CYP2D6 (ultra, intermediate or poor metabolizer), plus CYP2C19 (ultra, rapid or poor metabolizer) combined with normal CYP2D6

Population prevalence estimates from eTable2 for SLCO1B1, HLA-B:58*01 and VKORC1; and from eTable 4 for CYP2C9, CYP2C19 and CYP2D6.
eTable 9. Summary of Strong Level A Phenotype-Based Recommendation That the Patient Be Prescribed Alternative or Dose-Adjusted Therapy

| Drug          | Gene       | Phenotype                  | CPIC Recommendation                                                                 |
|---------------|------------|---------------------------|---------------------------------------------------------------------------------------|
| Allopurinol   | HLA-B*58:01| Presence of the variant    | Significantly increased risk of allopurinol-induced severe cutaneous adverse reaction - allopurinol contraindicated (Strong) |
| Clopidogrel   | CYP2C19    | Poor metabolizer          | Select alternative antiplatelet agent; increased risk of non-efficacy and adverse CV events (Strong) |
| Codeine       | CYP2D6     | Ultra-rapid metabolizer   | Avoid codeine use due to potential for toxicity (Strong) Considerations for alternative opioids - Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone, are not good alternatives because their metabolism is affected by CYP2D6 activity. |
|               | CYP2D6     | Poor Metabolizer          | Avoid codeine use due to lack of efficacy (Strong) Considerations for alternative opioids - Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone, are not good alternatives because their metabolism is affected by CYP2D6 activity. |
| Simvastatin   | SLCO1B1    | Intermediate function     | Prescribe a lower dose or consider an alternative statin due to increased myopathy risk (strong) - intermediate myopathy risk. |
|               | SLCO1B1    | Low function              | Prescribe a lower dose or consider an alternative statin -increased myopathy risk (strong) - high myopathy risk. |
| Warfarin      | VKORC1     | Increased sensitivity     | For patients who self-identify as non-African ancestry, strong data to support using a CYP2C9/VKORC1 pharmacogenetic algorithm to guide warfarin dosing. |
|               | CYP2C9     | Poor metabolizer          |                                                                                       |

Medications with a strong CPIC level A recommendation to either avoid or dose-adjust a medication based on available pharmacogenetic test results are included.
**eTable 10.** Estimation of the Proportions of Level A Drug Users at Risk of Drug Nonefficacy or Adverse Effects Described in Figure 3

| Drug                | Gene                  | Phenotype                     | Unique drug users (No.) | Projected w/ phenotype (%)<sup>a</sup> | Projected w/ phenotype (No.) | Total of actionable phenotypes by drug (No.)<sup>b</sup> | Proportion of all actionable variants by drug (%)<sup>c</sup> |
|---------------------|-----------------------|-------------------------------|-------------------------|---------------------------------------|----------------------------|------------------------------------------------------------|---------------------------------------------------------------|
| Allopurinol         | HLA-B*58:01           | Presence of the variant       | 215,055                 | 3.8%                                  | 8,172                      | 8,172                                                      | 100.0%                                                        |
| Clopidogrel PCI     | CYP2C19               | Poor metabolizer             | 51,094                  | 2.9%                                  | 1,482                      | 14,937                                                     | 9.9%                                                          |
|                     | CYP2D6                | Ultra-rapid metabolizer      | 528,159                 | 3.5%                                  | 18,486                     | 46,941                                                     | 39.4%                                                         |
| Codeine             | SLCO1B1               | Intermediate function        | 533,928                 | 23.4%                                 | 124,939                    | 136,599                                                    | 91.5%                                                         |
|                     | SLCO1B1               | Low function                 | 533,928                 | 2.2%                                  | 11,746                      | 136,599                                                    | 8.6%                                                          |
| Simvastatin         | SLCO1B1               | Increased sensitivity        | 174,400<sup>c</sup>     | 66.6%<sup>c</sup>                     | 116,151                    | 148,928 (all ancestries)                                   | 78.0%                                                         |
| Warfarin            | VKORC1                | (with projected European ancestry) | 174,400<sup>c</sup>     | 66.6%<sup>c</sup>                     | 116,151                    | 148,928 (all ancestries)                                   | 78.0%                                                         |
|                     | CYP2C9                | Poor metabolizer            | 174,400<sup>c</sup>     | 66.6%<sup>c</sup>                     | 116,151                    | 148,928 (all ancestries)                                   | 78.0%                                                         |

Abbreviations: PCI: percutaneous coronary intervention

Medications with a strong CPIC level A recommendation to either avoid or dose-adjust a medication based on available pharmacogenetic test results, genes and phenotypes associated with an increased risk of toxicity and/or adverse drug reaction in response to drug exposure, number of unique drug users for the drug in 2012-2017, projected prevalence and number of patients with specific phenotype at a high risk of adverse drug reaction and/or non-efficacy, total number of patients with an actionable phenotype.

<sup>a</sup>The percentage represents the proportion of Veterans prescribed this medication with the projected phenotype or genetic variant.

<sup>b</sup>From eTable 8.

<sup>c</sup>Warfarin only has a strong recommendation for patients identifying as non-African ancestry. There are additional recommendations for patients with African ancestry, but we limited our analyses to the projected European ancestry proportion of our population. Therefore, 85% of the 205,177 unique warfarin users are projected to be of European ancestry in our model (n=174,400). Using the values that 4.0% of patients of European ancestry are projected to be CYP2C9 poor metabolizers (eTable 4) and 65.2% of patients of European ancestry are projected to have actionable VKORC1 actionable genotypes (eTable 3), we projected the % actionable phenotypes of patients of European ancestry using the following equation: CYP2C9 poor*VKORC1 sens+CYP2C9 poor*VKORC1wt+VKORC1Sens*CYP2C9wt = 0.04*0.652 + 0.04*(1-0.652) + (1-0.04)*0.652 = 66.6% of patients with European ancestry are projected to have actionable phenotype.
**eFigure.** Result of the Sensitivity Analysis for the Projected Prevalence of Actionable Genotypes Under Different Population Models

Plot showing the distribution of estimates for the prevalence of PGX variants obtained under the six models (eTable 5)

AFR 15%, Model 1 with 15% patients of African ancestry and 85% of patients of European ancestry; AFR20%, Model 2, 20% patients of African ancestry and 80% of patients of European ancestry; AFR Models 3 and 4 models the admixture of African American patients with a 21% contribution of European ancestry; the 21% contribution was estimated based on the literature review summarized in eTable 4. Model 5 applies the variant frequencies for the African American in Southwest USA in the 1000 Genome Project with weights of 15% ASW/85% EUR. Model 6 tests the effect of accounting the contribution of populations from American origin, and models the population as 15% for AFR, 7% AMR (population from Americas), and 78% EUR.

Abbreviations: AFR: African ancestry; AMR: Americas; ASW, People with African Ancestry in Southwest USA; EUR, European ancestry.
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