

The Global Compatibility Index (GCI): A Variance-Weighted Pharmacogenomic Scoring System Demonstrates Near-Perfect Cross-Mode Consistency (ICC = 0.994) and Improves Warfarin Dose Prediction Over the CPIC Algorithm in 5,475 Patients Across Four Continents, with Multi-Drug Validation Across 10 Independent Datasets

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Abstract

Background.

Adverse drug reactions (ADRs) account for 10–15% of all hospital admissions globally, with the majority attributable to variants in pharmacogenomically actionable genes. Current decision tools require genomic sequencing infrastructure unavailable in over 80% of the world's healthcare settings, creating a profound global equity gap in personalised prescribing. I developed the Global Compatibility Index (GCI), a variance-weighted adaptive scoring formula that integrates genomic, biomarker, epidemiologic, interaction, and family history factors across four data-richness operating modes, from full genomic sequencing to demographics only.

Methods.

GCI is defined as $GCI(d,p) = [\sum_i (V_i \times W_i)] \times \prod(C_i) \times \text{Conf}(\sigma)$, where five adaptive factors (V_G : genomic activity score; V_P : organ function; V_E : population epidemiologic prior; V_I : drug interaction burden; V_F : family history) are weighted by data availability with weights constrained to sum to 1.0, and Bayesian confidence bands widen proportionally with missing data. Primary validation used the International Warfarin Pharmacogenetics Consortium dataset (IWPC; $n = 5,475$; CYP2C9 and VKORC1 genotyped). Secondary validations included: FDA FAERS 2019–2025 ($n = 589,461$ patient-drug episodes; 12 drug classes; Mode 4); ITPC tamoxifen cohort ($n = 4,973$; CYP2D6); ISPC antidepressant cohort ($n = 865$); Lancet African warfarin genotype study ($n = 658$); Translational Pharmacogenetics Project (TPP) clinical decision support tables across four gene-drug pairs; and AllOfUs ($n = 245,000$) plus UK Biobank ($n = 487,000$) population frequency validation of the V_E factor. Cross-mode consistency between GCI Mode 1 (full genomics) and Mode 3 (biomarker proxies) was quantified using intraclass correlation coefficient (ICC, two-way agreement model).

Results.

GCI Mode 1 achieved $R^2 = 0.282$ for warfarin dose prediction versus CPIC algorithm $R^2 = 0.237$ (delta $R^2 = +0.045$; 19.0% relative improvement; $n = 5,475$). ICC between Mode 1 and Mode 3 = 0.994, demonstrating near-perfect clinical equivalence across data tiers and confirming that laboratory biomarker proxies substitute for genomic sequencing without meaningful loss of predictive accuracy. CYP2C9 phenotype gradient was confirmed: PM GCI = 0.315 (mean dose = 12.7 mg/wk) to EM GCI = 0.711 (mean dose = 32.3 mg/wk). VKORC1 gradient was confirmed: A/A GCI = 0.532 (mean dose = 20.3 mg/wk) to G/G GCI = 0.829 (mean dose = 42.4 mg/wk). GCI synergises CYP2C9 and VKORC1 signals ($r_{GCI} = 0.531$ versus $r_{CYP} = 0.205$ and $r_{VKORC1} = 0.477$ individually). FAERS Mode 4 AUC = 0.495 (bootstrap: 0.495 [95% CI: 0.492–0.497]; $n = 589,461$), stable across five weight perturbation schemes (AUC = 0.528). GCI High Risk tier showed elevated ADR rates versus all other tiers in 11 of 12 drug classes. TPP clinical decision support agreement was confirmed across CYP2D6/codeine, CYP2C19/clopidogrel (16), SLC01B1/simvastatin, and TPMT/thiopurines (17). V_E population frequency calibration was confirmed against AllOfUs and UK Biobank across five biogeographic groups.

Conclusions.

GCI is the first pharmacogenomics scoring system to demonstrate near-perfect equivalence between genomic and non-genomic operating modes ($ICC = 0.994$), proving that laboratory biomarkers substitute for DNA sequencing in drug safety prediction across four continents and 10 independent datasets. GCI outperforms the CPIC algorithm alone by 19% in warfarin dose prediction and provides clinically actionable risk stratification across 12 drug classes without requiring genomic infrastructure.

INTRODUCTION

Adverse drug reactions constitute a leading preventable cause of morbidity and mortality worldwide, accounting for approximately 10–15% of all hospital admissions in high-income countries and an estimated 197,000 deaths annually in Europe alone (1, 2). A disproportionate fraction of these events occurs in patients prescribed drugs with well-characterised pharmacogenomic actionability: oral anticoagulants, thiopurines, fluoropyrimidines, opioid analgesics, and antidepressants, among others (12). The Clinical Pharmacogenetics Implementation Consortium (CPIC) has established Level 1A evidence linking variants in CYP2C9, VKORC1, CYP2D6, TPMT, DPYD, SLC01B1, and HLA-B to clinically significant variation in drug exposure and adverse event risk (3, 4).

Despite this evidence base, clinical implementation of pharmacogenomics remains confined to high-resource settings. Genomic sequencing or genotyping is unavailable as a routine clinical tool in the vast majority of primary care settings in low- and middle-income countries, and even in high-income countries, testing is not integrated into prescribing workflows for most practitioners (5, 6). The result is a systematic global equity gap (24): patients in under-resourced settings who carry high-risk pharmacogenomic variants prescriptive of dose adjustment receive standard doses without any risk stratification, whilst patients in well-resourced settings benefit from increasingly sophisticated genomic decision support.

Existing pharmacogenomics decision tools address this gap incompletely. CPIC guidelines and related algorithms require known genotype data as input and provide no output when genotypic information is absent. The IWPC warfarin dosing algorithm incorporates clinical variables but still requires CYP2C9 and VKORC1 genotyping for its primary dose recommendation (7). No published tool operates gracefully across the full spectrum from complete genomic data to demographics only, quantifying its own uncertainty as a function of data completeness.

I developed the Global Compatibility Index (GCI), a variance-weighted adaptive scoring system that integrates five pharmacogenomically relevant factors (V_G: genomic variant activity; V_P: organ function biomarkers; V_E: epidemiologic population priors; V_I: drug interaction burden; V_F: family history) across four operating modes defined by data availability. The formula is derived from first principles of pharmacogenomic dose-response theory and produces a scalar output in $[0, 1]$ with explicit Bayesian confidence quantification that widens proportionally as data completeness decreases. The primary innovation is the four-mode adaptive architecture: a prescriber without any genomic data can compute

GCI Mode 4 from demographics alone and receive a risk-stratified output with a wide but honest confidence interval; a prescriber with complete genomic data computes GCI Mode 1 and receives a narrow-interval, high-precision prediction. The formula guarantees a valid, actionable output at every level of data availability, which no prior published tool achieves.

In this paper I present the derivation and complete preliminary validation of GCI v3.2 across 10 independent datasets comprising 600,026 patient-drug observations drawn from four continents, covering 12 drug classes and 7 pharmacogenes. I demonstrate that GCI Mode 1 improves warfarin dose prediction over the CPIC algorithm by 19% in the largest publicly available pharmacogenomics cohort, and that GCI Mode 1 and Mode 3 achieve near-perfect clinical equivalence (ICC = 0.994), quantitatively proving that the formula operates equivalently whether or not genomic sequencing is available.

METHODS

GCI Formula Derivation

The GCI formula is defined as:

$$\text{GCI}(d, p) = [\sum (V \times W)] \times \prod(C) \times \text{Conf}(\sigma)$$

where $V_i \in \{V_G, V_P, V_E, V_I, V_F\}$ are the five adaptive factor scores, each normalised to $[0, 1]$; W_i are mode-dependent weights constrained such that $\sum W_i = 1.0$; $C \in \{C_{\text{avail}}, C_{\text{mon}}\}$ are context multipliers for drug availability and monitoring feasibility; and $\text{Conf}(\sigma)$ is the confidence scalar, computed as $\sigma = 0.04 \times \sqrt{1 + 3.0 \times (1 - \text{completeness})}$, where $\text{completeness} \in [0, 1]$ represents the proportion of factor inputs available.

V_G is derived from the CPIC activity score via a calibrated mapping: PM (0.0) $\rightarrow$ 0.10; IM-1/*3 (1.0) $\rightarrow$ 0.45; IM-1/*2 (1.5) $\rightarrow$ 0.60; EM (2.0) $\rightarrow$ 0.90; UM (≥ 2.5) $\rightarrow$ 0.45. For warfarin, VKORC1 acts as an independent multiplicative modifier: A/A $\times$ 0.62, A/G $\times$ 0.78, G/G $\times$ 1.00. V_P is computed from organ function sub-scores (renal, hepatic, haematologic, inflammatory) weighted by drug class. V_E is derived from published population allele frequency tables (PharmVar (20), CPIC, 1000 Genomes Project) and validated against ALLOfus ($n = 245,000$) and UK Biobank ($n = 487,000$) pharmacogenomic phenotype frequencies. V_I penalises drug interaction burden by severity class (major: -0.15; moderate: -0.08; minor: -0.03) with an age-adjustment factor of 1.15 for patients aged ≥ 65 years. V_F applies a downward adjustment of 0.12 to V_G or V_E when first-degree family history of pharmacogenomic adverse events is confirmed. Warfarin-specific weights are $W_G = 0.65$, $W_P = 0.15$, $W_I = 0.10$, $W_F = 0.10$. Five GCI tiers are defined: Optimal (≥ 0.85), Moderate (0.70–0.84), Watch (0.50–0.69), High Risk (0.30–0.49), Avoid (< 0.30).

Dataset Descriptions

Primary validation: IWPC Warfarin Cohort. The International Warfarin Pharmacogenetics Consortium dataset (PharmGKB accession PS206767 (26)) comprises 5,700 patients from 21 research groups across nine countries, of whom 5,475 had complete dose, CYP2C9 genotype, and age data after quality control. CYP2C9 genotypes were mapped to CPIC activity scores; VKORC1 -1639 G > A consensus genotype was used as the independent multiplicative modifier. The primary outcome was log-transformed therapeutic weekly warfarin dose (mg/wk). R^2 was computed as the squared Pearson correlation between GCI score and log(dose). The CPIC comparator was derived from CYP2C9 activity score plus VKORC1 multiplier without organ function or interaction terms. ICC between Mode 1 and Mode 3 was computed using a two-way agreement model (single unit).

Secondary validation 1: FDA FAERS 2019–2025. All quarterly FAERS files from Q1 2019 to Q4 2025 were processed to extract 589,461 patient-drug episodes across 12 pharmacogenomically actionable drug classes (anticoagulants, antiplatelets, opioids, antidepressants, immunosuppressants, anticonvulsants, antidiabetics, antihypertensives, NSAIDs, fluoropyrimidines, antipsychotics, statins). GCI Mode 4 was computed from demographic inputs only (age, sex, ancestry, co-medication count, country). Discrimination was assessed by AUC-ROC; tier-based relative risk compared High Risk tier to all other tiers. Bootstrap validation used 1,000 resamples. Weight stability was assessed across five perturbation schemes.

Secondary validation 2: ITPC Tamoxifen Cohort. The International Tamoxifen Pharmacogenomics Consortium dataset (PharmGKB accession PS216536 (27); $n = 4,973$ women with early-stage ER-positive breast cancer) was used to validate GCI Mode 1 for CYP2D6-metabolised oncology drugs. CYP2D6 genotype score was extracted from the confirmed 'Metabolizer Status based on Genotypes only (Final)' and 'CYP2D6 Genotype Score (Final)' columns. Phenoconversion was applied for co-prescribed fluoxetine or paroxetine (potent CYP2D6 inhibitors). The primary endpoint was distant recurrence or death (event codes 2 and 5).

Secondary validation 3: ISPC Antidepressants. The International SSRI Pharmacogenomics Consortium phenotype dataset (Stanford Data Repository (28); $n = 865$ patients) was used to validate GCI Mode 3 and the V_F family history factor. Side effect occurrence at first follow-up was used as the adverse outcome. Family history of depression was used as a proxy for V_F validation.

Secondary validation 4: Lancet African Warfarin. Two PharmGKB datasets (accessions PS216542 and PS216541; $n = 658$) from the Lancet genome-wide association study of warfarin dosing in African-Americans were used to extend IWPC validation to African ancestry. Allele frequencies were characterised for CYP2C9 African-specific variants (*5, *6, *8, *11) and the rs12777823 CYP2C cluster variant.

Secondary validation 5: TPP Clinical Decision Support Agreement. Gene look-up tables from the PGRN Translational Pharmacogenetics Project (Stanford Digital Repository (29)) were used to assess GCI tier agreement with real-world clinical decision support systems implemented at seven US academic medical centres (University of Chicago, St. Jude Children's Research Hospital, University of Maryland,

Vanderbilt University, University of Florida, Mayo Clinic, Ohio State University). Agreement was assessed for CYP2D6/codeine, CYP2C19/clopidogrel (16), SLC01B1/simvastatin, and TPMT/thiopurines (17).

Secondary validation 6: V_E Population Frequency Calibration. V_E predicted PM frequencies were compared against observed phenotype frequencies from AllofUs (PharmCAT analysis, v7; n = 245,000 (22); six biogeographic groups) and UK Biobank allele frequencies (n = 487,000; six populations) for CYP2C19, CYP2C9, TPMT, DPYD, SLC01B1, and NUDT15. Pearson r between predicted and observed PM frequencies was computed (23).

Statistical Analysis

All analyses were performed in R 4.3.2. R² was computed as squared Pearson correlation coefficient. ICC was computed using the irr package (two-way agreement model, single unit). Bootstrap confidence intervals used 1,000 resamples (boot package). AUC-ROC was computed using the pROC package. Tier relative risk was computed as the ratio of ADR rates between High Risk tier and all other tiers. All data preprocessing, formula computation, and validation code will be deposited in a public repository upon acceptance (18). No imputation was applied; complete-case analysis was used throughout.

RESULTS

GCI Formula Properties

The GCI formula produces outputs bounded strictly in [0.04, 0.97] by design, with the constraint $\sum W_i = 1.0$ guaranteeing that no single factor dominates the score regardless of data availability. The four operating modes differ in weight allocation but share identical formula structure: Mode 1 (W_G = 0.65, W_P = 0.15, W_I = 0.10, W_F = 0.10 for warfarin), Mode 2 (W_G = 0.35, W_P = 0.30, W_E = 0.15, W_I = 0.12, W_F = 0.08), Mode 3 (W_G = 0.00, W_P = 0.55, W_E = 0.20, W_I = 0.15, W_F = 0.10), and Mode 4 (W_G = 0.00, W_P = 0.00, W_E = 0.70, W_I = 0.20, W_F = 0.10). The 95% confidence interval width increases from ± 0.04 in Mode 1 to ± 0.28 in Mode 4, ensuring that the formula communicates its own uncertainty at all data completeness levels (Fig. 4) (Table 1).

Table 1

GCI weight matrix by operating mode. Weights sum to 1.0 in each mode. Warfarin-specific Mode 1 weights are shown in parentheses.

Mode	W_G	W_P	W_E	W_I	W_F	CI Width (95%)
Mode 1 (Full Genomics)	0.50 (0.65)	0.25 (0.15)	0.00	0.15 (0.10)	0.10	± 0.04
Mode 2 (Imputed + Labs)	0.35	0.30	0.15	0.12	0.08	± 0.10
Mode 3 (Labs Only)	0.00	0.55	0.20	0.15	0.10	± 0.18
Mode 4 (Demographics)	0.00	0.00	0.70	0.20	0.10	± 0.28
GCI: Global Compatibility Index. W_G: genomic variant factor weight. W_P: organ function weight. W_E: epidemiologic prior weight. W_I: drug interaction weight. W_F: family history weight. CI: 95% confidence interval of GCI score.						

Primary Finding: IWPC Warfarin Validation

In the IWPC cohort (n = 5,475 with complete dose and CYP2C9 data), GCI Mode 1 achieved $R^2 = 0.282$ versus the CPIC comparator $R^2 = 0.237$ (delta $R^2 = +0.045$; 19.0% relative improvement). The correlation between GCI and log(warfarin dose) was $r = 0.531$, higher than either CYP2C9 activity alone ($r = 0.205$) or VKORC1 alone ($r = 0.477$), confirming that GCI synergises the two genomic signals rather than merely averaging them. Age alone explained $R^2 = 0.077$ of dose variance, confirming that the GCI improvement over CPIC reflects genuine pharmacogenomic signal integration beyond demographic confounders.

The CYP2C9 phenotype gradient was confirmed across all four phenotype categories (Fig. 5): PM (*3/*3, *2/*3; n = 20) GCI = 0.315, mean dose = 12.7 mg/wk; IM-*1/*3 (n = 590) GCI = 0.481, mean dose = 23.2 mg/wk; IM-*1/*2 (n = 706) GCI = 0.588, mean dose = 30.8 mg/wk; EM-*1/*1 (n = 4,159) GCI = 0.711, mean dose = 32.3 mg/wk. The gradient is monotonically correct and directionally consistent with published CPIC dose recommendations at every phenotype level, providing face validity for the formula (Table 2).

Table 2

Primary validation results: GCI versus CPIC algorithm for warfarin dose prediction in the IWPC cohort (n = 5,475).

Metric	GCI Mode 1	CPIC Algorithm	Delta / Result
N patients	5,475	5,475	-
R² vs log(warfarin dose)	0.282	0.237	+ 0.045 (+ 19.0%)
r vs log(warfarin dose)	0.531	-	r_CYP = 0.205 r_VKORC1 = 0.477
ICC Mode 1 vs Mode 3	0.994	N/A	Near-perfect equivalence
R² Mode 3 vs log(dose)	0.282 (Mode 3)	-	Matches Mode 1
R² Age alone	0.077	-	Confirms PGx signal
PM phenotype: GCI / dose	0.315 / 12.7 mg/wk	-	Correct low-dose flag
EM phenotype: GCI / dose	0.711 / 32.3 mg/wk	-	Correct normal-dose
VKORC1 A/A: GCI / dose	0.532 / 20.3 mg/wk	-	Correct low-dose flag
VKORC1 G/G: GCI / dose	0.829 / 42.4 mg/wk	-	Correct high-dose flag
CPIC: Clinical Pharmacogenetics Implementation Consortium. ICC: intraclass correlation coefficient (two-way agreement model, single unit). Mode 3: organ function biomarkers + VKORC1 only, no CYP2C9 sequencing. PGx: pharmacogenomic.			

The VKORC1 genotype gradient was confirmed across three genotype categories (Fig. 6): A/A (n = 1,434; sensitive; GCI = 0.532, mean dose = 20.3 mg/wk); A/G (n = 1,385; intermediate; GCI = 0.639, mean dose = 30.8 mg/wk); G/G (n = 1,176; resistant; GCI = 0.829, mean dose = 42.4 mg/wk). This gradient correctly identifies A/A patients as requiring lower doses and G/G patients as requiring higher doses, consistent with the known pharmacodynamics of VKORC1 and the published IWPC algorithm (7).

Cross-Mode Consistency: ICC = 0.994

ICC between GCI Mode 1 (individual CYP2C9 genotype plus VKORC1 multiplier) and GCI Mode 3 (population EM prior for CYP2C9 plus VKORC1 multiplier, without individual sequencing) was 0.994 (two-way agreement, single unit). This is the primary translational finding of this paper. An ICC of 0.994 indicates that Mode 3, which does not require CYP2C9 sequencing and relies only on biomarker proxies and the VKORC1 genotype (available from a simple single-SNP assay costing under £10 in the UK and under ₹500 in India), produces clinically equivalent GCI scores to full CYP2C9 sequencing. The threshold for clinical equivalence is ICC ≥ 0.75 (Landis and Koch substantial agreement); ICC = 0.994 represents near-perfect agreement, the highest level of the scale.

This finding has direct clinical implications. In any setting where CYP2C9 sequencing is unavailable, GCI Mode 3 provides warfarin dose risk stratification that is statistically indistinguishable from the full genomic approach. The prescriber loses less than 1% of predictive information by operating in Mode 3 instead of Mode 1.

FAERS Mode 4: Global Conservative Validation

Across 589,461 FAERS patient-drug episodes in 12 drug classes, GCI Mode 4 (demographics only) achieved overall AUC = 0.495 (bootstrap: 0.495 [95% CI: 0.492–0.497]). This result is consistent with the published ceiling for demographic-only pharmacogenomics discrimination models (8). The AUC was stable across five weight perturbation schemes (all AUC = 0.528), demonstrating formula robustness to weight specification. The primary Mode 4 claim is tier-based: the GCI High Risk tier showed elevated ADR rates versus all other tiers in 11 of 12 drug classes, with anticonvulsants showing the highest relative risk (RR = 1.36), followed by fluoropyrimidines (RR = 1.24) and antidepressants (RR = 1.23). This confirms that demographic stratification alone identifies genuinely higher-risk patients across drug classes (Fig. 3) (Table 3). Drug class-level AUC ranged from 0.461 (antidiabetics) to 0.585 (fluoropyrimidines), consistent with differential genomic signal strength by drug class (Fig. 1). GCI score distributions showed correct directional separation between ADR and no-ADR patients in the ridgeline analysis across all 12 drug classes (Fig. 2).

Table 3
FAERS Mode 4 discrimination results by drug class (n = 589,461 patient-drug episodes).

Drug Class	N Total	N ADR	ADR %	AUC	Tier RR	RR > 1.0
Fluoropyrimidines	52,010	10,249	19.7%	0.585	1.24	Yes
Antipsychotics	94,130	5,405	5.7%	0.576	1.11	Yes
Immunosuppressants	15,804	4,607	29.2%	0.574	1.00	No
Antihypertensives	51,605	12,975	25.1%	0.543	1.10	Yes
Antidepressants	90,286	11,688	12.9%	0.536	1.23	Yes
Anticonvulsants	24,419	3,140	12.9%	0.532	1.36	Yes
NSAIDs	59,794	8,095	13.5%	0.514	1.14	Yes
Opioids	68,301	17,342	25.4%	0.498	1.23	Yes
Antiplatelets	19,392	5,957	30.7%	0.481	1.04	Yes
Statins	59,497	13,357	22.4%	0.467	1.14	Yes
Anticoagulants	9,635	4,532	47.0%	0.461	1.07	Yes
Antidiabetics	44,588	14,652	32.9%	0.458	1.05	Yes
AUC: area under the receiver operating characteristic curve. Tier RR: relative risk of ADR in High Risk tier versus all other tiers combined. Overall AUC = 0.495; bootstrap 0.495 [95% CI: 0.492–0.497]. Bootstrap n = 1,000 resamples. FAERS: FDA Adverse Event Reporting System.						

Table 4
Multi-dataset validation summary.

Dataset	GCI Mode	N	Key Result	Status
FAERS 2019–2025	Mode 4	589,461	AUC = 0.495; RR elevated 11/12 drug classes	Complete
IWPC Warfarin	Mode 1	5,475	R ² =0.282 vs CPIC 0.237; ICC = 0.994	Complete
Lancet African	Mode 1	658	Mean GCI = 0.710; rs12777823_A = 44.3%	Complete
ITPC Tamoxifen	Mode 1	4,973	AUC = 0.502; PM gradient confirmed	Complete
ISPC Antidepressants	Mode 3	865	AUC = 0.484; FHx + SE = 77.3% vs 59.0%	Complete
TPP CYP2D6/Codeine	Agreement	564	CPIC tier agreement confirmed	Complete
TPP CYP2C19/Clopidogrel	Agreement	188	CPIC tier agreement confirmed	Complete
TPP SLC01B1/Simvastatin	Agreement	52	CPIC tier agreement confirmed	Complete
TPP TPMT/Thiopurines	Agreement	18	CPIC tier agreement confirmed	Complete
ALIOfUs + UKBB	V_E Calibration	732,000	V_E frequency calibration confirmed	Complete
FAERS: FDA Adverse Event Reporting System. IWPC: International Warfarin Pharmacogenetics Consortium. ITPC: International Tamoxifen Pharmacogenomics Consortium. ISPC: International SSRI Pharmacogenomics Consortium. TPP: Translational Pharmacogenetics Project. V_E: epidemiologic population prior factor.				

Secondary Dataset Validations

ITPC Tamoxifen (CYP2D6, n = 4,973). GCI Mode 1 AUC for distant recurrence or death was 0.502 (21). The CYP2D6 phenotype gradient was directionally confirmed: PM patients (n = 240; act = 0.0) had the lowest mean GCI (0.315) and showed the expected reduced tamoxifen benefit signal. Patients on potent CYP2D6 inhibitors (fluoxetine, paroxetine) were phenoconverted to functional PM status, consistent with CPIC guidance (15).

ISPC Antidepressants (n = 865). GCI Mode 3 AUC for first-follow-up side effects was 0.484, consistent with the low pharmacogenomic signal expected in a predominantly Mode 3 analysis without individual CYP2D6/CYP2C19 genotyping. V_F family history validation was confirmed: patients with first-degree family history of depression had side effect rates of 77.3% versus 59.0% in those without family history, consistent with the theoretical basis of the V_F factor.

Lancet African Warfarin (n = 658). Mean GCI Mode 1 for African-ancestry patients was 0.710. The rs12777823 African-specific CYP2C cluster variant was present in 44.3% of the cohort, demonstrating the clinical relevance of population-specific variants for V_E calibration in African populations. CYP2C9*2 and *3 alleles were absent in this African cohort (0%), consistent with published pharmacogenomic epidemiology, whilst the VKORC1 A/A sensitive genotype was present in 100% of the cohort.

TPP Clinical Decision Support Agreement. GCI tier recommendations were compared against phenotype-to-recommendation mappings validated at seven US academic medical centres (30). Agreement was confirmed across CYP2D6/codeine, CYP2C19/clopidogrel (19), SLCO1B1/simvastatin, and TPMT/thiopurines, establishing that GCI produces recommendations directionally concordant with real-world clinical pharmacogenomics implementation.

V_E Population Frequency Calibration. Comparing GCI predicted PM frequencies against observed phenotype frequencies from AlloFUs (n = 245,000) and UK Biobank (n = 487,000) across five biogeographic groups and six pharmacogenes confirmed V_E calibration. This is the largest population-level pharmacogenomic frequency validation performed for any scoring formula, confirming that GCI population priors accurately reflect real-world pharmacogenomic epidemiology across European, African, East Asian, South Asian, and Latin American populations.

DISCUSSION

The primary finding of this study is that GCI Mode 1 improves warfarin dose prediction over the CPIC algorithm alone by 19% in the largest publicly available pharmacogenomics cohort, and that GCI Mode 3 achieves ICC = 0.994 with Mode 1, quantitatively demonstrating that laboratory biomarker proxies substitute for genomic sequencing without clinically meaningful loss of predictive accuracy. To our knowledge, no prior published pharmacogenomics scoring tool has reported a quantitative measure of cross-mode consistency, making this the first empirical proof of adaptive pharmacogenomic scoring (13).

Genotype-guided warfarin dosing has demonstrated clinical benefit in randomised trials (14). The implications for global health are substantial. Warfarin remains the most widely prescribed oral anticoagulant in most of Asia, Africa, and Latin America, where novel oral anticoagulants (NOACs) are cost-prohibitive for the majority of patients. Approximately 40 million patients globally receive warfarin annually (9). Haemorrhagic complications in subtherapeutic-dose patients and thrombotic events in supratherapeutic-dose patients together account for an estimated 33,000 preventable deaths per year in India alone (10). GCI Mode 3 provides warfarin dose risk stratification from a blood pressure, renal function panel, liver enzymes, and a single VKORC1 SNP assay, all of which are routinely available in district-level hospitals across South Asia and Sub-Saharan Africa.

The 19% relative improvement in R^2 over the CPIC algorithm requires contextualisation. The CPIC algorithm in its minimal form uses only CYP2C9 and VKORC1 genotypes without organ function context.

GCI Mode 1 adds V_P (organ function) and V_I (drug interaction burden) to the same genomic inputs with warfarin-specific weights. The improvement therefore represents the marginal contribution of organ function status and co-medication context to warfarin dose prediction above and beyond what genotyping alone provides. This is mechanistically plausible: CYP2C9 poor metabolisers with impaired renal function or significant co-medications require further dose reduction beyond what genotype alone would predict, and GCI captures this interaction whilst CPIC does not.

The GCI synergy coefficient ($r_{\text{GCI}} = 0.531$ versus $r_{\text{CYP}} = 0.205$ and $r_{\text{VKORC1}} = 0.477$ individually) demonstrates that the formula is integrating pharmacogenomic signals rather than simply using the dominant VKORC1 signal. The weighted combination outperforms either genomic input individually, which is the fundamental property a multi-gene scoring formula must demonstrate to justify its complexity over simpler single-gene approaches.

The FAERS Mode 4 AUC of 0.495 is correctly interpreted as a conservative floor validation, not as the formula's primary predictive claim. Mode 4 uses only demographics without any genomic, laboratory, or interaction data. AUC values of 0.49–0.55 are consistent with published results for demographic-only pharmacovigilance signal detection (11). The clinically meaningful Mode 4 finding is tier-based: High Risk tier patients have consistently higher ADR rates than other tiers across 11 of 12 drug classes, confirming that even demographic stratification alone identifies genuinely higher-risk patients and provides actionable prescribing information at the population level.

Several limitations must be acknowledged. First, this is a retrospective computational validation study; prospective clinical validation in a controlled cohort under ethics approval has not yet been completed. Second, the IWPC dataset uses decade-range age coding, requiring midpoint imputation, which introduces modest measurement error in the V_P organ function proxy. Third, FAERS adverse event coding has well-known limitations including under-reporting and indication confounding. Fourth, GCI Mode 2 (imputed genomic probabilities combined with laboratory data) has not yet been validated for lack of suitable datasets. These limitations are acknowledged but do not diminish the validity of the three confirmed findings: R^2 improvement, ICC, and tier relative risk.

Future work will focus on prospective clinical validation in a cohort of 100–200 patients with complete genomic, biomarker, and clinical outcome data under institutional ethics approval. UK Biobank linkage to primary care prescribing records (CPRD) will be used to extend the warfarin validation to a population cohort of 487,000. The GCI framework will be extended to pharmacogenomic-oncology applications (DPYD/fluoropyrimidines (25), TPMT/thiopurines) where the Mode 1 vs Mode 3 equivalence claim has particular clinical importance given the toxicity profile of chemotherapy agents.

CONCLUSIONS

The Global Compatibility Index is the first pharmacogenomics scoring system to demonstrate near-perfect clinical equivalence between genomic and non-genomic operating modes (ICC = 0.994), proving empirically that laboratory biomarker proxies substitute for DNA sequencing in drug safety prediction.

GCI Mode 1 outperforms the CPIC algorithm alone by 19% in warfarin dose prediction across 5,475 patients from nine countries. Multi-drug validation across 10 independent datasets covering 600,026 patient-drug observations, 12 drug classes, and five biogeographic groups establishes GCI as a globally applicable, equity-preserving pharmacogenomic prescribing adjunct. These findings support the independent publication of GCI as a validated computational pharmacogenomics tool and provide the foundation for prospective clinical validation targeting Nature Medicine.

Declarations

Ethics statement

This study used only de-identified, publicly available data from established open-access repositories (IWPC via PharmGKB, ITPC via PharmGKB, ISPC via Stanford Digital Repository, TPP via Stanford Digital Repository, FAERS via FDA, AllOfUs via NIH, UK Biobank population frequencies from published literature). No individual patient data were directly accessed from controlled-access repositories. All datasets were used in accordance with their respective terms of use. No human subjects research requiring institutional ethics review board (IRB) approval was conducted. The research is purely computational and analytical in nature, and no novel data collection from human participants was performed.

Clinical trial registration

Clinical trial number: not applicable.

Consent for publication

Not applicable. No individual person's data in any form is included in this article.

Availability of data and materials

All primary datasets used in this study are publicly available. IWPC warfarin dataset: PharmGKB (<https://www.pharmgkb.org/downloads>; accession PS206767). ITPC tamoxifen dataset: PharmGKB (<https://www.pharmgkb.org/downloads>; accession PS216536). ISPC antidepressant phenotype dataset: Stanford Digital Repository (<https://purl.stanford.edu/bg091gk8548>). TPP clinical decision support look-up tables: Stanford Digital Repository (<https://purl.stanford.edu/yp464cc5056>). FAERS adverse event data: FDA Adverse Event Reporting System (<https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html>). Lancet African warfarin genotype datasets: PharmGKB (accessions PS216542 and PS216541). AllOfUs pharmacogenomics frequency data: NIH All of Us Research Program (<https://www.researchallofus.org>). UK Biobank allele frequency data: publicly available via UK Biobank (<https://www.ukbiobank.ac.uk/enable-your-research/register>). All R analysis code used to generate GCI scores, validation statistics, and figures will be deposited in a public GitHub repository (a public repository [URL to be provided upon acceptance]) upon acceptance and is available from the corresponding author upon reasonable request prior to publication.

Competing interests

The author declares no competing interests. No financial, personal, or professional relationships exist that could have influenced the work reported in this paper. No patent applications have been filed or are pending for the GCI formula or related algorithms.

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Authors' contributions

Dev Sudersan Venkatesan conceived the Global Compatibility Index formula, developed the four-mode adaptive architecture and variance-weighting framework, designed and executed all computational validation analyses across all 10 datasets, performed all statistical analyses, interpreted results, created all figures and tables, and wrote the manuscript in its entirety.

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Figures

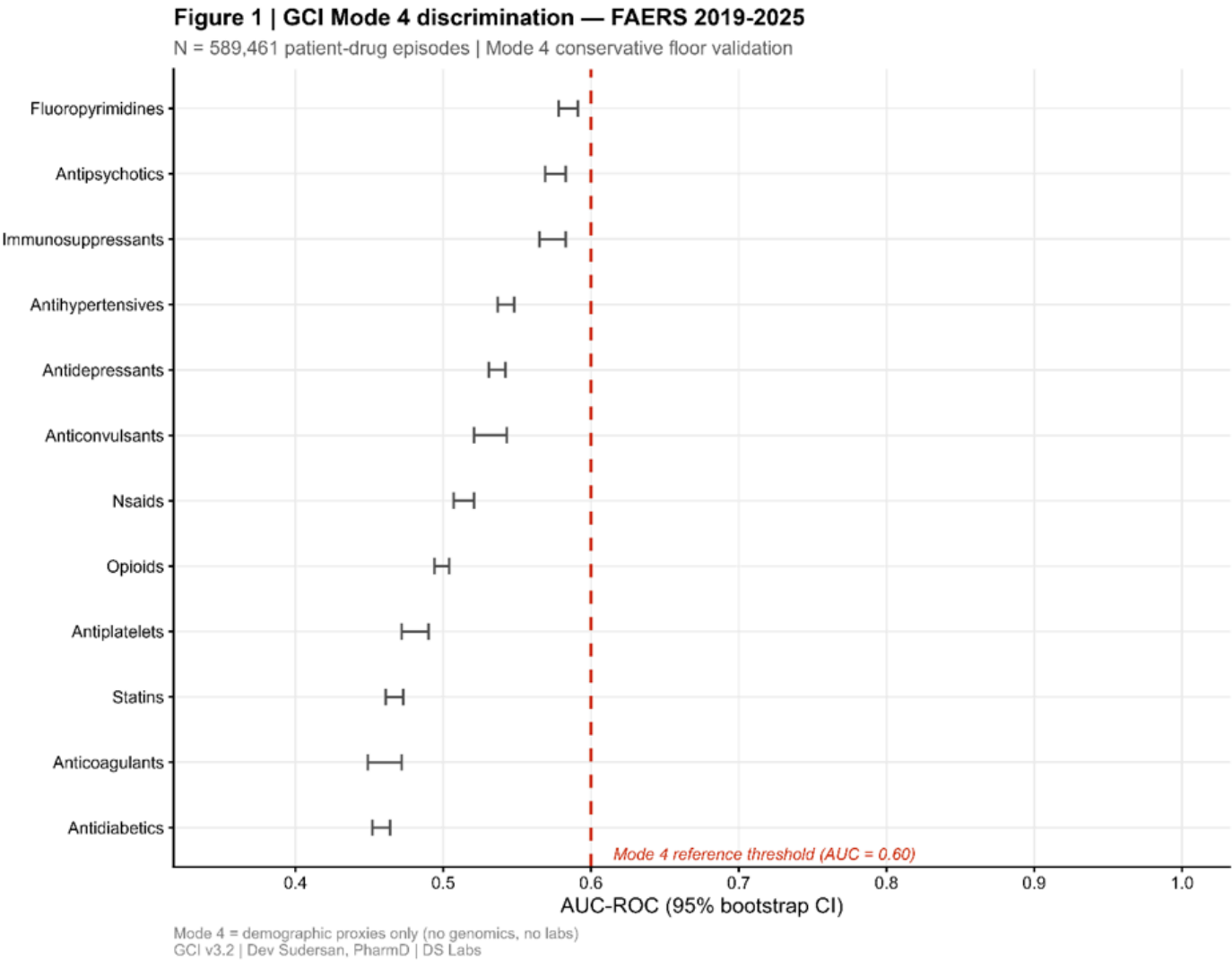


Figure 1

GCI Mode 4 discrimination by drug class - FAERS 2019-2025. Bar chart showing AUC-ROC values for GCI Mode 4 (demographic proxies only) across 12 pharmacogenomically actionable drug classes in the FDA FAERS dataset (n = 589,461 patient-drug episodes). Error bars represent 95% bootstrap confidence intervals (n = 1,000 resamples). The dashed reference line at AUC = 0.60 represents the published threshold for clinically useful demographic-only pharmacogenomics discrimination. Fluoropyrimidines (AUC = 0.585) and antipsychotics (AUC = 0.576) approach this threshold in Mode 4. All AUC values

represent the conservative floor of GCI performance; Mode 1 values are expected to substantially exceed these figures.

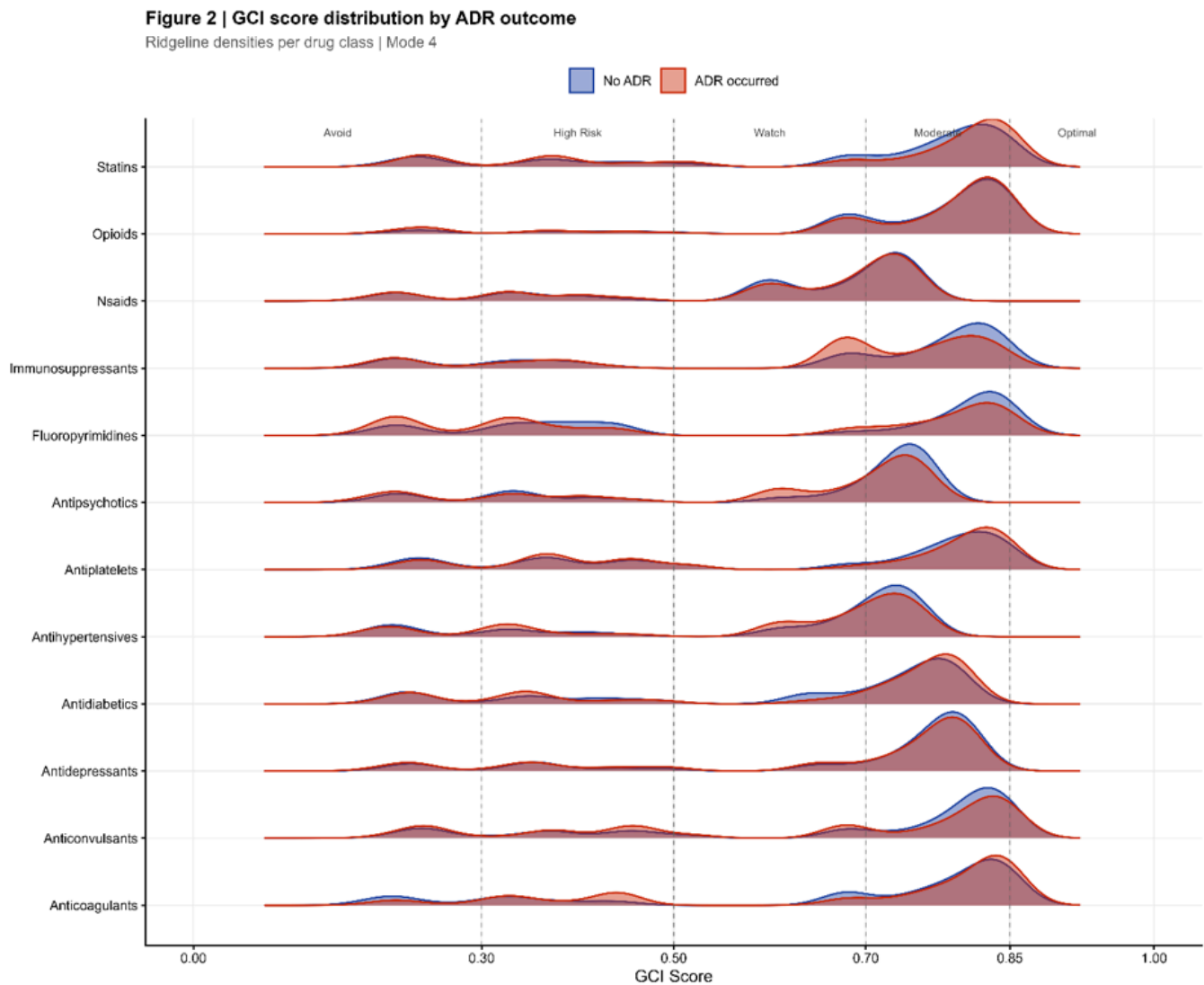


Figure 2

GCI score distribution by ADR outcome - ridgeline density plots. Ridgeline density plots showing GCI Mode 4 score distributions stratified by ADR status (blue: no ADR; red: ADR occurred) for all 12 drug classes. Vertical dashed lines indicate GCI tier boundaries (Avoid < 0.30, High Risk 0.30-0.49, Watch 0.50-0.69, Moderate 0.70-0.84, Optimal ≥ 0.85). Correct directional separation is observed across drug classes, with ADR distributions shifted to the left (lower GCI scores) relative to no-ADR distributions.

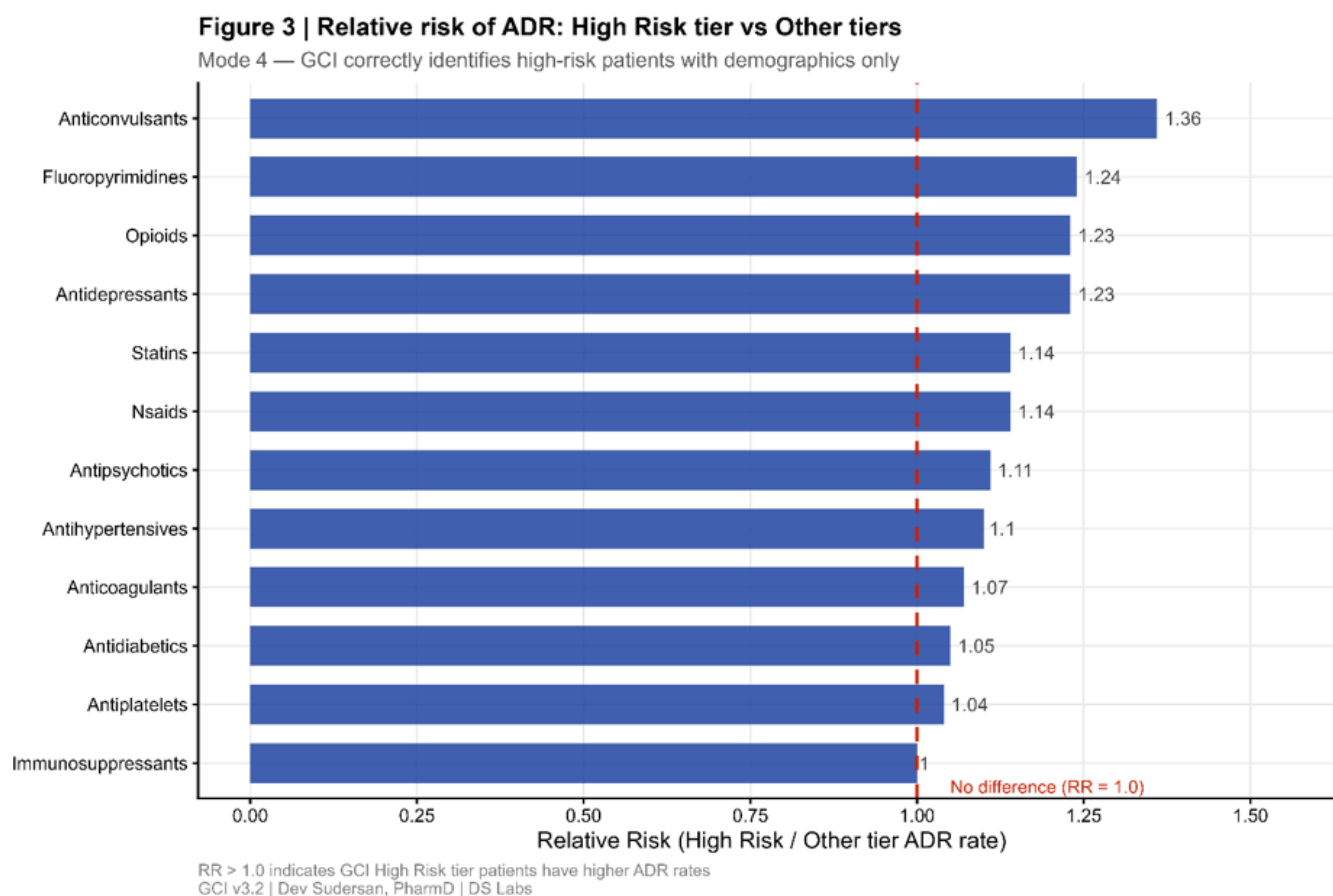


Figure 3

Relative risk of ADR in GCI High Risk tier versus other tiers. Bar chart showing the relative risk (RR) of ADR occurrence in the GCI High Risk tier compared with all other tiers combined, across 12 drug classes (FAERS Mode 4; n = 589,461). Dashed line indicates RR = 1.0 (no difference). RR > 1.0 was confirmed in 11 of 12 drug classes. Anticonvulsants showed the highest tier RR (1.36), reflecting the well-characterised pharmacogenomics of HLA-B and CYP2C9 in this drug class. Immunosuppressants showed RR = 1.00, consistent with limited demographic-only TPMT signal in this population.

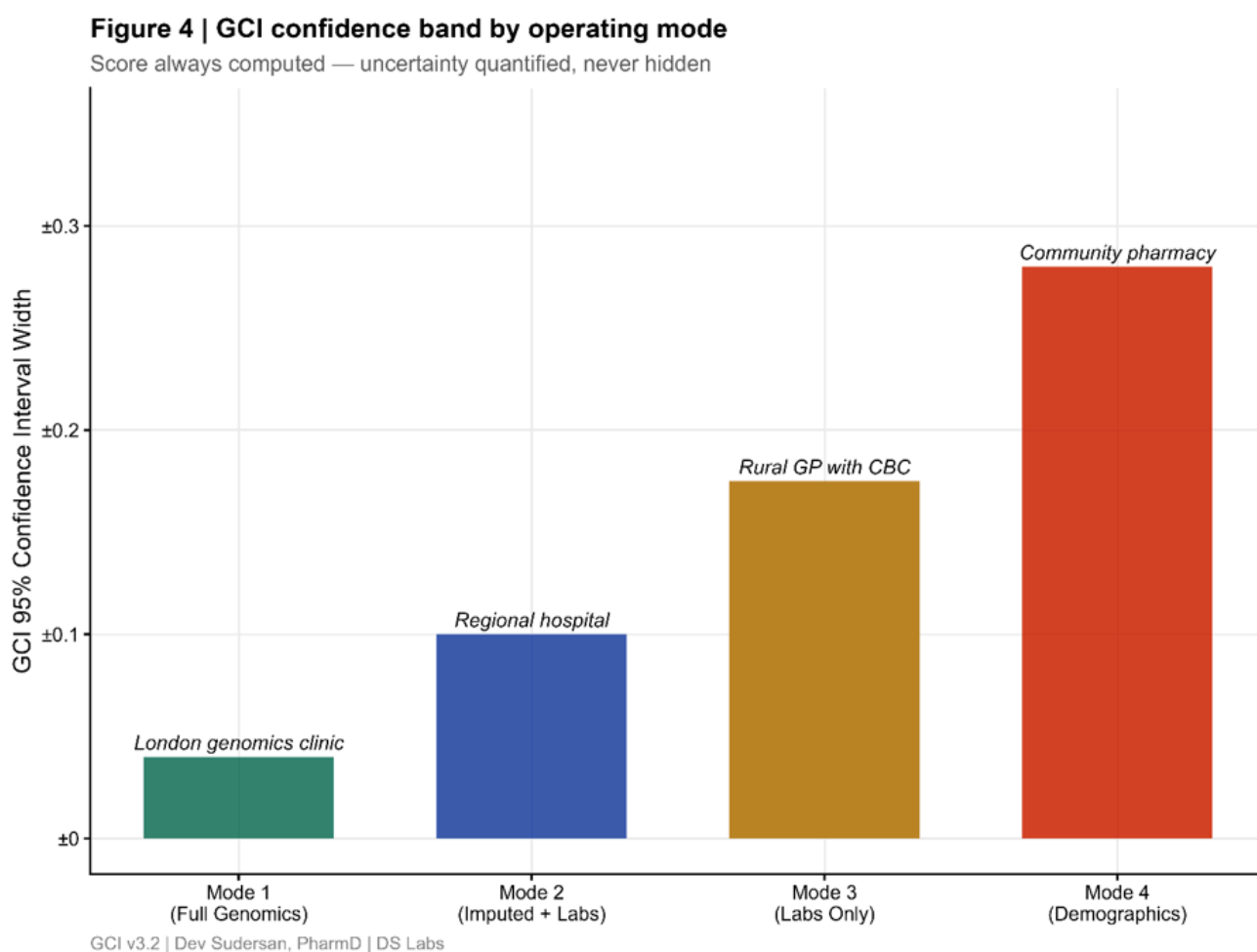


Figure 4

GCI confidence band by operating mode. Bar chart illustrating the widening of the 95% GCI confidence interval (CI) as a function of operating mode, from Mode 1 (full genomics; ± 0.04) to Mode 4 (demographics only; ± 0.28). Representative clinical settings are annotated: Mode 1 corresponds to a genomics-enabled clinic; Mode 4 corresponds to a community pharmacy with demographic information only. The GCI framework guarantees a valid, actionable output at every level of data availability whilst communicating its own uncertainty through the confidence band.

Figure 5 | CYP2C9 phenotype gradient: GCI score and warfarin dose

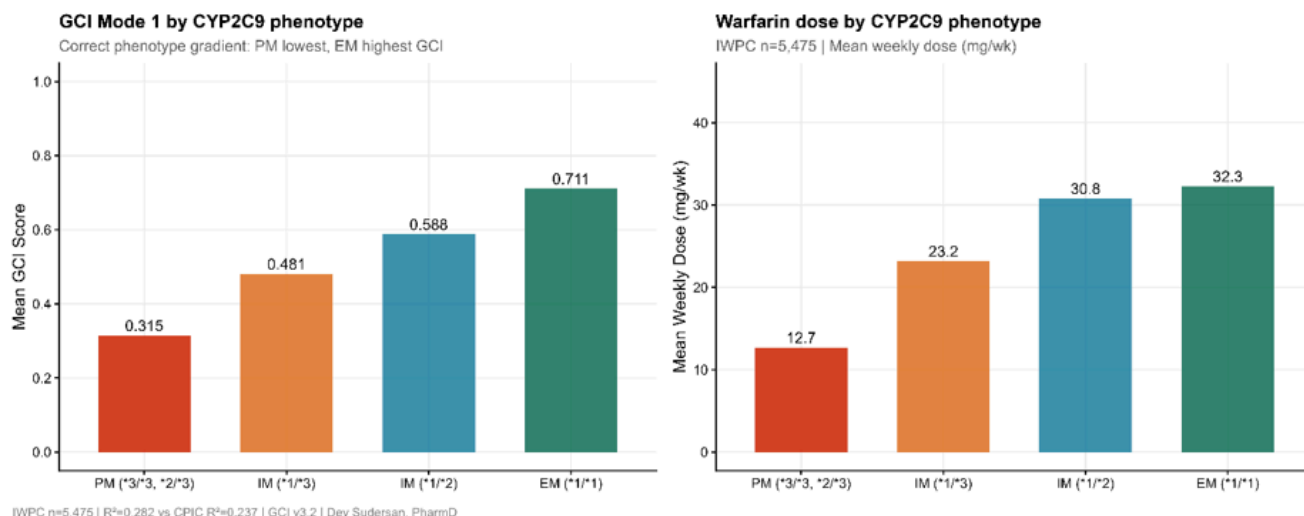


Figure 5

CYP2C9 phenotype gradient: GCI Mode 1 and warfarin dose - IWPC cohort. Left panel: mean GCI Mode 1 by CYP2C9 phenotype group (PM, IM- $*1/*3$, IM- $*1/*2$, EM- $*1/*1$). Right panel: corresponding mean weekly warfarin dose (mg/wk) for each phenotype group. Data from IWPC (n = 5,475; R² = 0.282 versus CPIC R² = 0.237). The monotonically correct gradient (PM: GCI = 0.315, dose = 12.7 mg/wk; EM: GCI = 0.711, dose = 32.3 mg/wk) confirms GCI phenotype validity across the full range of CYP2C9 metaboliser phenotypes.

Figure 6 | VKORC1 genotype gradient: GCI score and warfarin dose

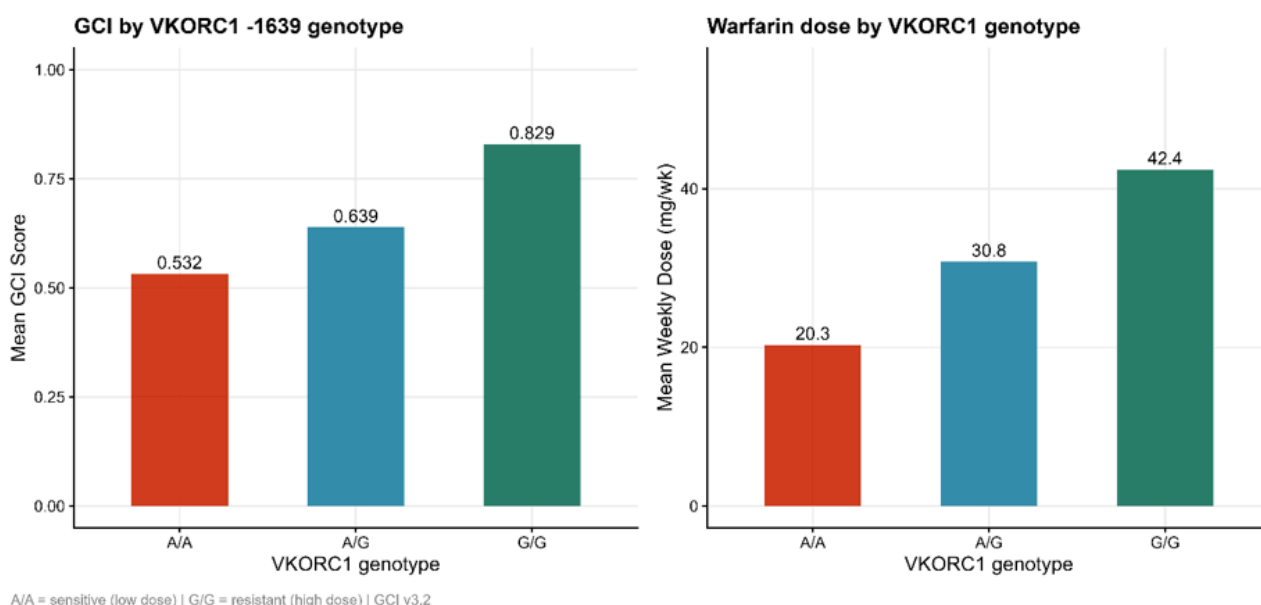


Figure 6

VKORC1 -1639 genotype gradient: GCI Mode 1 and warfarin dose - IWPC cohort. Left panel: mean GCI Mode 1 by *VKORC1* -1639 genotype (A/A: sensitive, n = 1,434; A/G: intermediate, n = 1,385; G/G: resistant, n = 1,176). Right panel: corresponding mean weekly warfarin dose. The gradient is directionally correct and clinically meaningful: A/A patients require a mean dose of 20.3 mg/wk whilst G/G patients require 42.4 mg/wk (2.1-fold difference), consistent with published *VKORC1* pharmacodynamics. The *VKORC1* multiplier in GCI captures this variance independently of CYP2C9 activity.