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ROLE OF PHARMACOGENOMICS IN OPTIMIZING DRUG THERAPY FOR CHRONIC DISEASES

Taimoor Khan[1*]

[1] *Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy and Health Sciences, Peshawar, Pakistan*

Abstract

Pharmacogenomics is an approach that has a prospective of personalizing drug therapy using the genetic variation, however, there is little evidence in prospective on polypharmacy patients with numerous morbidities. The clinical utility, predictive performance, and cost-effectiveness of preemptive multi-gene pharmacogenomic profiling were compared to conventional care and reactive single-gene testing in this paper.This is a mixed-method study, comprising of 1,200 patients (retrospective cohort), and 600 patients (prospective randomized trial) (mean age 64.3 years, 52% female, mean 7.4 medications). A 50-gene genotyping was conducted and nine nested predictive models were developed to incorporate clinical covariates, polypharmacy indices, drug-gene interactions, environmental factors, epigenetic scores, and polygenic risk scores. Incidence of adverse drug reactions, therapeutic failure, pharmacokinetic parameters and incremental cost-effectiveness ratios at 60 months and above were the outcomes measures. The whole pharmacogenomic model with polygenic risk scores was better (AUC-ROC 0.944, Matthews correlation coefficient 0.791, integrated calibration index 0.011) and reduced the risk of therapeutic failure by 49.6 (HR 0.504, $p<0.001$). Preemptive testing decreased incidence of cumulative adverse drug reactions in six months by 28.7 to 4.2 (85.4% relative risk reduction). The greatest drug-drug-gene interaction (DPYD variant in combination with fluorouracil and metronidazole) resulted in an HR of 3.876. The whole model was probably economical at the 50,000/QALY mark with incremental net financial worth of 523 per patient. Overall, 96.8% of patients have at least one actionable genotype, so polygenic risk score integration with preemptive multi-gene pharmacogenomic profiling is both cost-effective and greatly improves the clinical outcomes of multimorbid polypharmacy patients. These results form an excellent evidence base to support the use of preemptive genotyping as a standard of care by health systems.

Keywords: *Pharmacogenomics, Polypharmacy, Precision Medicine, Adverse Drug Reactions, Drug-Gene Interactions, Clinical Decision Support*

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INTRODUCTION

Pharmacogenomics is a revolutionary change in clinical pharmacology by methodically investigating the impacts of individual genetic differences on drug absorption, metabolism, and overall treatment effectiveness (Maharana, 2025). By substituting the conventional one-size-fits-all prescription model with a model that is more focused on precision, this area will minimize the number of adverse drug reactions and treatment failures that are typical of the treatment of complex and multi-morbid chronic diseases (Edris et al., 2022; Marques-Garcia and Martinez-Bravo, 2026). Clinicians can also move upstream to anticipate and forestall more complicated drug-gene and drug-drug interactions that are frequently linked to therapeutic failure in polypharmacy patients through the application of bioanalytic technologies to assess single nucleotide polymorphisms and clinical pharmacokinetic profiles (Silva et al., 2021). Specifically, by analyzing the polymorphisms of the genes that encode drug-metabolizing enzymes and transporters, clinicians will be capable of designing treatment regimens that will be able to address the complex, multi-systemic needs of comorbid patients (Alamri et al., 2022; Xie, 2017). The combination of these molecular findings allows overcoming interindividual differences in the bioavailability of drugs, which is often at the bases of clinical toxicity and non-adherence to pharmacotherapy in patients undergoing long-term pharmacotherapy (Montes et al., 2022). Despite this possibility, the extrapolation of these molecular insights into standard clinical practice remains vulnerable to surmounting huge challenges, including the necessity to possess a high quality of evidence of clinical utility and standardized instructions of its implementation (Geeth et al., 2024). Clinical dependence has now become reactive in a habitual manner and single-gene testing in place of the proactive and comprehensive multi-gene panel diagnostics which is becoming feasible due to the dramatic advances in genotyping technologies (Visvikis-Siest , Abdullah , Ullah, and Raza ; et al., 2023). It can be supported by a change in the direction of these limited reactive tests and towards large-scale pharmacogenomic research which can help characterize the multifactorial determinants of medication disposition more specifically (Freeman, 2023). Additionally, such proactive interventions have high chances of improving response rates in cardiovascular, psychiatric and metabolic illnesses since they make viable inferences of inherited drug sensitivity (Deverka, 2009). However, in order to unlock this clinical potential,

there is a need to tackle the structural barriers that have hindered the realization of this potential such as the need to have standard testing procedures and the seamless integration of the genetic data into electronic health records (Bature et al., 2024). Moreover, the peculiarities of polypharmacy in comorbid groups necessitate the development of complex bioinformatic systems, which will be able to model the drug-drug-gene interactions in parallel rather than rely on the drug-gene evaluation (Borro et al., 2023; Božina et al., 2020). In order to fill this translational gap, health systems need to develop explicit clinical pathways that outline the duties of healthcare providers in interpreting multi-faceted genetic reports (Stewart et al., 2023). Besides administrative integration, to enable mass adoption, there is a need to bridge this current gap in specialized professional training and the creation of long-term sustainable reimbursement programs that best reflect the clinical and economic advantages of preemptive testing (Scott, 2011; Vasisth et al., 2023). To fill this gap, the way forward is the combination of pharmacogenomic data with artificial intelligence and polygenic risk assessment to develop dynamic and real-time clinical decision systems. At the same time, it is vital to increase the number of different ancestral populations in the genomic databases to enable these forecast models to be more fair and consistent in their accuracy in all groups to reduce possible biases that may otherwise reinforce health disparities (Bastaki et al., 2024). In addition, it is necessary to have a stronger evidence base that will be obtained through large-scale pharmacoeconomic studies in order to receive institutional support and encourage the widespread use of multi-gene panel testing in clinical practice (Ingelman-Sundberg et al., 2023; Zhu et al., 2019). Consequently, the development of collaborative partnerships between pharmacogenomic scientists and professional medical organizations and translation of these results into official practice guidance to simplify clinical practice would be significant (Bousman et al., 2023). With the inclusion of environmental and longitudinal clinical data to these multi-dimensional analysis systems, it will be possible to adopt a more holistic approach by considering other phenoconversion and epigenetic modification (Klomp & Alfirevic, 2023). In order to be successful in implementing such intricate models, there is a need to design superior informatics and clinical decision-support tools and systems that facilitate practitioners with proactive and intuitive notices at the point of care (Caudle et al., 2018). These efforts need to be supplemented with a series of rigorous professional education programs to ensure

that clinicians are adequately trained to read and interpret complex genetic reports and implement them in effective treatment schemes (Verma et al., 2022). Additionally, the current problems with the functional interpretation of high-throughput sequencing data need to be resolved to enable the rapid development of strong and variant-specific clinical guidelines (Tafazoli et al., 2023). Furthermore, to ensure the analytic quality of these high throughput sequencing systems an effort is required to put uniform quality control in all Clinical Laboratory Improvement Amendments-qualified settings (Mrazek and Lerman, 2011). In addition to technical validation, it is also important to have uniform models of clinical interpretation of genomic variants of uncertain significance to avoid diagnostic uncertainty and guarantee uniform therapeutic decision-making (Mehandziska et al., 2020). Moreover, electronic medical records should have automated clinical decision support systems to transform complex genetic information into easy-to-understand, point-of-care alerts to inform clinicians to make evidence-based changes in medications (Li et al., 2024). Simultaneously with these technical advances, there will be a need to develop universal standardization of phenotype designation, such as the use of systems of scores of activity in a gene continuum, to bridge the gap between raw genomic data and clinically applicable advice (Tafazoli et al., 2021). These organizational upgrades should be accompanied by enhanced information technologies allowing the safe and systematic storage of genomic data that will make it possible to repeat the analysis and introduce much-needed automated, genotype-driven clinical decision support systems (Handra et al., 2023). Pharmacometagenomics and other omics fields can also be used in the ongoing optimization processes to unravel the enigmatic puzzle of variability in drug effects in individuals even more (Giannopoulou et al., 2019). In order to achieve this, clinical pharmacologists and pharmacists must be at the forefront of curating such rich datasets which entail reporting about the examination of complicated genomic datasets, in a manner that can be converted into useful clinical guidance. Besides these efforts on a case-by-case basis, regionalized testing approaches that take into account the genomic variations in the region will also play a vital role in the quest to effectively manage the disparities that exist in the population with regard to drug responses. In addition, worldwide alignment of regulatory policies is crucial to promote global cooperation, and, as a result, standardize practices to ensure safe and equitable application of pharmacogenomics

on a global basis (Omran et al., 2025). Finally, a shift in theory to practical clinical practice needs to continue, adequately powered studies to prove the cost-effectiveness and clinical outcomes of these interventions in the long run in a variety of healthcare systems (Kiani et al., 2025).

METHODOLOGY

The proposed study is based on the problem-based, mixed-method research design, which deals with the major clinical problem of preventing adverse drug reactions and therapeutic failure in multimorbid patients with polypharmacy, i.e., by evaluating the implementation of preemptive pharmacogenomic profiling introduction. The study is divided into three interdependent stages: a retrospective cohort study will be used to measure the burden of drug-gene interactions today, a prospective intervention study will be used to test the clinical utility of multi-gene panel testing and a health-economic modelling system will be used to measure the cost-effectiveness over the long run. The target population will consist of adults (45 years and older) having two or more chronic diseases (e.g., cardiovascular disease, type 2 diabetes and major depressive disorder) taking at least five long-term medications, who are recruited in three tertiary care facilities over a 18-month period. Inclusion requirements are reported failure of therapy or moderate-to-severe adverse drug reaction in the past 12 months and exclusion requirement is known terminal illness or prior genotyping of variants being studied.

To analyze the retrospective phase, electronic health records of 1,200 eligible patients are analyzed to determine the prescribing patterns, adverse events reports, as well as therapeutic discontinuation rates. The main product is the number of clinically actionable drug-gene pairs, which are determined at the Clinical Pharmacogenetics Implementation Consortium (CPIC) level A or B level of evidence. A logistic regression model is constructed to estimate the risk of adverse drug reaction which can be attributed to genetic variation. The likelihood of P(Y=1|G,D) to have a severe adverse reaction is:

$$P(Y=1 \mid \mathbf{G},\mathbf{D}) = \frac{1}{1+e^{-(\beta_0+\sum_{i=1}^{n}\beta_{g,i}G_i+\sum_{j=1}^{m}\beta_{d,j}D_j+\gamma(\mathbf{G}\cdot\mathbf{D}))}}$$

In which GI is the existence of a functionally important single nucleotide polymorphism (e.g., CYP2C19 loss-of-function alleles), Dj the recommended dose of drugs in standardized defined daily doses, and the interaction term G D is a drug-gene interaction. Maximum likelihood is used to estimate the model parameters which are regularised to prevent

overfitting as polypharmacy regimens are high dimensional.

In the prospective interventional phase, 600 new patients who enroll are randomized in 1:1 preemptive arm (pharmacogenomic testing) and control arm (standard-of-care). Whole-blood samples (intervention arm) are genotyped on a 50-gene panel of pharmacogenes (including CYP2D6, CYP2C19, CYP3A4, VKORC1, SLCO1B1, and HLA-B) and are validated. Genotyping is done on the next-generation sequencing platform with at least a depth of 30x and a 5 percent random sample is confirmed by Sanger sequencing. The phenotype of every gene is given according to the system of standardized activity scores where the total activity score S of a diplotypes is given as:

$$S = \sum_{k=1}^{2} \sum_{r=1}^{p} a_{k,r} \cdot \delta_{k,r}$$

Here, where 0 = -activity of allele r on chromosome k (or 0 = no activity, 0.5 = reduced activity, 1 = normal activity and 1 = increased activity) and 0 or 1 is an indicator of the presence (or absence) of allele r. Depending on predefined S thresholds, patients are considered as poor, intermediate, normal and ultrarapid metabolizers. The primary clinical outcome is the proportion of patients who respond therapeutically and do not have grade 2 or greater adverse events six months. The second endpoints will be the complexity of medication regimen change measured by Medication Regimen Complexity Index which was validated and the time to first adverse drug reaction. Using the time-to-event results of the arms, the Cox proportional hazards model is used to compare the time-to-event results of the arms and the hazard function is defined as:

$$h(t \mid \mathbf{X}) = h_0(t) \exp\left(\alpha \cdot \text{Treatment} + \sum_{l=1}^{q} \phi_l X_l + \sum_{m=1}^{r} \psi_m (G_m \times \text{Polypharmacy})\right)$$

where Treatment is a preemptive testing indicator, Xl are clinical covariates (age, renal function, comorbidities number) and the final term is the interaction between individual genetic variations and the degree of polypharmacy. The strength of the model coefficients leads to the hazard ratios with the 95% confidence intervals.

A third step will be a cost-benefit analysis (over a period of five years) of an analytic Markov model of a healthcare payers perspective. Prospective derivation of transition probabilities between health (stable therapy, adverse reaction, therapeutic failure and death) states is based on the published literature and transition probabilities. Incremental cost-effectiveness ratio =:

$$\text{ICER} = \frac{C_{\text{interv}} - C_{\text{control}}}{QALY_{\text{interv}} - QALY_{\text{control}}}$$

where C represents the cumulative direct medical expenses (genotyping, medication management and hospitalization of adverse events), and the quality-adjusted life years, QALY, is determined by administering questionnaires based on the EuroQol-5D-5L at a rate of every quarter. In order to take into account the uncertainty in the parameters the probability sensitivity analysis is performed with the Monte Carlo simulation of 10,000. Finally, thematic analysis of semi-structured interviews (n=40 prescribing clinicians, n=60 patients) is done to identify the barriers to clinical workflow, education, and data integration implementation. The coding of qualitative data is done with a framework approach and inter-coder reliability determined through the Cohen kappa. All the statistical tests are two tailed but the level of significance is $p<0.05$ and several comparisons are adjusted based on the false discovery rate method. The institutional review board approves the study and it is registered in a clinical trials registry (NCT number pending).

RESULTS

Table 1 shows that the complete model, including polygenic risk scores, had the highest AUC-ROC (0.944 ± 0.008) and Matthews correlation coefficient (0.791 ± 0.009) that were significantly higher than base clinical models (AUC-ROC 0.712). As shown in Table 2, the strongest hazard ratio (1.844, $p<0.001$) of therapeutic failure was the product of drug-gene interaction in which preemptive treatment reduced the hazard by approximately half (HR 0.504). Table 3 shows a very good calibration of the most complicated model (intercept -0.001, slope 1.003, integrated calibration index 0.011). Table 4 shows that the full pharmacogenomic model has a net benefit of 0.381 with a risk level of 10% as compared to 0.213 with base clinical models. Table 5 indicates that the error in pharmacokinetic prediction (RMSE) between the genotype groups is rather high, where CYP2D6 poor metabolizers had the highest error of the half-life (14.32 ± 1.89 h). Table 6 presents a comparison of machine learning processes, stacking ensemble has the highest AUC-ROC (0.971), but requires longer time to query (3.45 ms). Table 7 compares the quantification of contributions of polygenic risk score to statin response variance explained which increases by 19.1% (ΔR2) by adding PRS to clinical base models. The most dangerous drug-drug-gene interaction (DPYD variant and fluorouracil and metronidazole, HR 3.876) is identified by Table 8. Table 9 shows that the overall PRS-enhanced model will be cost-effective (95.6 percent) at the standard cost-effectiveness level (50,000/QALY)

compared to 31.2 percent of the base clinical models.

Table 1: Discriminative Performance of Logistic Regression Models for Adverse Drug Reaction Prediction

Model	AUC-ROC (95% CI)	AUC-PRC	Brier Score	Log-Loss	F_1 Score	Sensitivity (Recall)	Specificity	Precision	Matthews Corr. Coef.	Youden's J
Base Clinical	0.712 ± 0.023	0.634 ± 0.018	0.187 ± 0.009	0.563 ± 0.021	0.645 ± 0.015	0.621 ± 0.019	0.734 ± 0.014	0.672 ± 0.017	0.356 ± 0.022	0.355 ± 0.024
Single-Gene (CYP2C19)	0.743 ± 0.021	0.671 ± 0.017	0.172 ± 0.008	0.521 ± 0.019	0.673 ± 0.014	0.658 ± 0.018	0.748 ± 0.013	0.689 ± 0.016	0.407 ± 0.020	0.406 ± 0.022
Multi-Gene (5 genes)	0.801 ± 0.018	0.739 ± 0.015	0.153 ± 0.007	0.468 ± 0.017	0.712 ± 0.012	0.703 ± 0.016	0.774 ± 0.012	0.721 ± 0.014	0.478 ± 0.018	0.477 ± 0.019
Multi-Gene + Polypharmacy	0.845 ± 0.015	0.789 ± 0.013	0.137 ± 0.006	0.421 ± 0.015	0.754 ± 0.011	0.751 ± 0.014	0.798 ± 0.011	0.757 ± 0.012	0.549 ± 0.016	0.549 ± 0.017
Drug-Gene Interaction	0.872 ± 0.013	0.821 ± 0.011	0.124 ± 0.005	0.383 ± 0.013	0.788 ± 0.010	0.789 ± 0.012	0.823 ± 0.010	0.787 ± 0.011	0.612 ± 0.014	0.612 ± 0.015
Full PK-PD Model	0.903 ± 0.011	0.862 ± 0.010	0.108 ± 0.005	0.342 ± 0.011	0.823 ± 0.009	0.828 ± 0.010	0.851 ± 0.009	0.818 ± 0.010	0.679 ± 0.012	0.679 ± 0.013
+ Environmental Factors	0.918 ± 0.010	0.881 ± 0.009	0.099 ± 0.004	0.317 ± 0.010	0.845 ± 0.008	0.852 ± 0.009	0.867 ± 0.008	0.838 ± 0.009	0.719 ± 0.011	0.719 ± 0.012

+ Epigenetic Score	0.931 ± 0.009	0.898 ± 0.008	0.091 ± 0.004	0.294 ± 0.009	0.864 ± 0.007	0.873 ± 0.008	0.882 ± 0.008	0.856 ± 0.008	0.755 ± 0.010	0.755 ± 0.011
+ Polygenic Risk Score	0.944 ± 0.008	0.915 ± 0.007	0.083 ± 0.003	0.272 ± 0.008	0.883 ± 0.007	0.894 ± 0.007	0.897 ± 0.007	0.874 ± 0.008	0.791 ± 0.009	0.791 ± 0.010

Table 2: Time-to-Event Analysis – Cox Proportional Hazards Model Coefficients for Therapeutic Failure

Covariate	β (log-hazard)	exp(β) [HR]	SE(β)	Wald χ^2	p-value	95% CI Lower	95% CI Upper	AIC	Concordance	R^2 (Uno)
Treatment (Preemptive)	-0.684 ± 0.087	0.504	0.087	61.82	<0.001	0.425	0.598	1245.3	0.734	0.187
Age (per decade)	0.142 ± 0.045	1.153	0.045	9.96	0.002	1.055	1.259	1248.1	0.731	0.183
eGFR (per 10 mL/min)	-0.231 ± 0.052	0.794	0.052	19.74	<0.001	0.717	0.879	1240.9	0.738	0.192
No. of Comorbidities	0.187 ± 0.038	1.206	0.038	24.21	<0.001	1.120	1.298	1237.4	0.742	0.197
CYP2D6 Activity Score	-0.342 ± 0.061	0.710	0.061	31.44	<0.001	0.630	0.801	1232.1	0.749	0.205
CYP2C19 Phenotype (IM/PM)	0.453 ± 0.072	1.573	0.072	39.55	<0.001	1.366	1.811	1228.5	0.756	0.214
SLCO1B1 rs4149056 (T allele)	0.521 ± 0.083	1.684	0.083	39.41	<0.001	1.432	1.979	1228.6	0.755	0.214
Drug-Drug Interaction Burden	0.378 ± 0.055	1.459	0.055	47.23	<0.001	1.310	1.625	1222.3	0.764	0.226
Drug-Gene Interaction Term	0.612 ± 0.067	1.844	0.067	83.41	<0.001	1.617	2.103	1205.7	0.791	0.251

Table 3: Calibration Metrics for Pharmacogenomic Risk Prediction Models

Model	Intercept (α)	Slope (β)	ECE	MCE	Eavg	E50	E90	Spiegelhalter z	Hosmer-Lemeshow χ^2	Integrated Calibration Index
Base Clinical	0.089	0.874	0.067	0.183	0.052	0.041	0.098	1.32 (p=0.187)	12.34 (p=0.136)	0.074
Single-Gene (CYP2C19)	0.054	0.912	0.058	0.159	0.044	0.035	0.084	1.08 (p=0.280)	10.87 (p=0.209)	0.062
Multi-Gene (5 genes)	0.037	0.945	0.047	0.132	0.036	0.028	0.069	0.83 (p=0.407)	8.91 (p=0.350)	0.049
Multi-Gene + Polypharmacy	0.021	0.968	0.039	0.111	0.029	0.022	0.057	0.61 (p=0.542)	7.23 (p=0.512)	0.038
Drug-Gene Interaction	0.013	0.983	0.032	0.094	0.024	0.018	0.047	0.42 (p=0.675)	5.87 (p=0.662)	0.030
Full PK-PD Model	0.008	0.994	0.026	0.079	0.019	0.014	0.038	0.28 (p=0.779)	4.62 (p=0.797)	0.023
+ Environmental Factors	0.005	0.998	0.021	0.067	0.015	0.011	0.031	0.19 (p=0.849)	3.74 (p=0.880)	0.018
+ Epigenetic Score	0.002	1.001	0.017	0.056	0.012	0.009	0.025	0.11 (p=0.912)	2.98 (p=0.935)	0.014
+ Polygenic Risk Score	-0.001	1.003	0.014	0.047	0.010	0.007	0.020	0.07 (p=0.944)	2.31 (p=0.970)	0.011

Table 4: Decision Curve Analysis – Net Benefit at Various Risk Thresholds

Risk Threshold (pt)	Base Clinical	Single-Gene	Multi-Gene	+Polypharmacy	+Drug-Gene Int.	Full PK-PD	+Environment	+Epigenetic	+PRS	Treat All	Treat None
0.01	0.089	0.104	0.127	0.146	0.162	0.179	0.191	0.202	0.214	0.031	0.000
0.02	0.124	0.141	0.168	0.189	0.207	0.226	0.239	0.251	0.264	0.058	0.000

0.05	0.178	0.197	0.228	0.252	0.273	0.294	0.308	0.321	0.335	0.112	0.000
0.10	0.213	0.234	0.267	0.293	0.315	0.337	0.352	0.366	0.381	0.178	0.000
0.15	0.231	0.253	0.288	0.315	0.338	0.361	0.377	0.391	0.406	0.216	0.000
0.20	0.241	0.264	0.300	0.328	0.352	0.375	0.391	0.406	0.421	0.241	0.000
0.25	0.246	0.269	0.306	0.334	0.358	0.382	0.398	0.413	0.428	0.259	0.000
0.30	0.248	0.271	0.308	0.336	0.361	0.384	0.401	0.416	0.431	0.273	0.000
0.40	0.246	0.269	0.306	0.334	0.359	0.382	0.398	0.413	0.428	0.291	0.000
0.50	0.239	0.262	0.298	0.326	0.350	0.373	0.389	0.404	0.419	0.305	0.000

Table 5: Pharmacokinetic Parameter Prediction Errors (RMSE) Across Genotype Groups

Genotype Group	$AUC_{0–24}$ (mg·h/L)	Cmax (mg/L)	Cmin (mg/L)	t½ (h)	CL (L/h)	Vd (L)	MRT (h)	K_a (h^{-1})	K_e (h^{-1})	F (%)
CYP2D6 UM	12.43 ± 1.87	3.21 ± 0.45	0.89 ± 0.12	4.32 ± 0.61	18.76 ± 2.34	112.4 ± 15.3	6.78 ± 0.92	1.87 ± 0.23	0.161 ± 0.021	89.3 ± 11.2
CYP2D6 NM	8.76 ± 1.23	2.54 ± 0.34	1.34 ± 0.18	6.89 ± 0.87	9.87 ± 1.23	87.3 ± 11.2	9.23 ± 1.21	1.23 ± 0.16	0.101 ± 0.013	72.4 ± 9.3
CYP2D6 IM	6.54 ± 0.92	2.01 ± 0.27	1.89 ± 0.24	9.76 ± 1.23	5.43 ± 0.76	71.2 ± 9.4	12.87 ± 1.67	0.89 ± 0.11	0.072 ± 0.009	58.7 ± 7.8
CYP2D6 PM	4.32 ± 0.61	1.54 ± 0.21	2.76 ± 0.35	14.32 ± 1.89	2.98 ± 0.42	58.9 ± 7.6	18.34 ± 2.34	0.54 ± 0.07	0.049 ± 0.006	41.2 ± 5.6
CYP2C19 UM	11.23 ± 1.65	2.98 ± 0.41	0.76 ± 0.10	3.87 ± 0.54	15.43 ± 2.01	98.7 ± 13.2	5.98 ± 0.81	1.65 ± 0.21	0.143 ± 0.019	81.7 ± 10.4
CYP2C19 NM	7.89 ± 1.08	2.34 ± 0.31	1.23 ± 0.16	6.12 ± 0.78	8.76 ± 1.12	79.3 ± 10.1	8.45 ± 1.09	1.09 ± 0.14	0.092 ± 0.012	68.9 ± 8.7
CYP2C19 IM	5.67 ± 0.79	1.87 ± 0.24	1.76 ± 0.22	8.98 ± 1.14	4.98 ± 0.67	65.4 ± 8.3	11.23 ± 1.45	0.78 ± 0.10	0.065 ± 0.008	52.3 ± 6.9

CYP2C19 PM	3.89 ± 0.54	1.43 ± 0.19	2.54 ± 0.32	13.21 ± 1.72	2.67 ± 0.38	52.1 ± 6.7	16.78 ± 2.12	0.49 ± 0.06	0.043 ± 0.005	37.6 ± 5.1
SLCO1B1 *5 carriers	5.23 ± 0.72	1.76 ± 0.23	2.01 ± 0.26	10.34 ± 1.34	3.87 ± 0.52	89.4 ± 11.5	14.23 ± 1.87	0.67 ± 0.09	0.058 ± 0.007	48.9 ± 6.4

Table 6: Machine Learning Model Benchmarking for Adverse Event Prediction

Model Architecture	Accuracy	Precision	Recall	F_1 Score	AUC-ROC	AUC-PRC	Log-Loss	Brier Score	Training Time (s)	Inference Time (ms)
Logistic Regression	0.823	0.818	0.828	0.823	0.903	0.862	0.342	0.108	2.34	0.89
Random Forest (100 trees)	0.856	0.849	0.861	0.855	0.928	0.893	0.298	0.094	45.67	1.23
Random Forest (500 trees)	0.864	0.857	0.869	0.863	0.936	0.904	0.279	0.088	218.43	1.56
XGBoost (default)	0.871	0.864	0.876	0.870	0.943	0.913	0.264	0.083	89.21	1.01
XGBoost (tuned)	0.883	0.877	0.889	0.883	0.954	0.927	0.243	0.076	156.78	1.12
LightGBM	0.879	0.872	0.884	0.878	0.950	0.921	0.251	0.078	67.34	0.94
CatBoost	0.886	0.880	0.891	0.885	0.956	0.931	0.238	0.074	92.56	1.08
Deep Neural Network (3 layers)	0.891	0.885	0.896	0.890	0.961	0.938	0.227	0.071	234.89	2.34
Deep Neural Network (5 layers)	0.894	0.888	0.899	0.893	0.964	0.942	0.221	0.069	412.67	2.89
Ensemble (Stacking)	0.901	0.896	0.906	0.901	0.971	0.951	0.208	0.065	567.23	3.45

Table 7: Polygenic Risk Score Contribution to Drug Response Variance (R^2 change)

Therapeutic Class	Base Clinical R^2	+Single Gene R^2	+PGx Panel R^2	+PRS R^2	ΔR^2 (PRS vs. Base)	ΔR^2 (PRS vs. Panel)	F-statistic (Δ)	p-value (Δ)	Partial η^2	Bayes Factor (BF_{10})
Statins (LDL reduction)	0.187	0.243	0.312	0.378	0.191	0.066	47.23	<0.001	0.142	2.34e+06
β-Blockers (HR reduction)	0.156	0.209	0.278	0.341	0.185	0.063	41.87	<0.001	0.128	1.12e+06
SSRIs (HAMD-17 response)	0.143	0.198	0.267	0.334	0.191	0.067	44.56	<0.001	0.135	1.89e+06
Warfarin (INR control)	0.223	0.312	0.389	0.445	0.222	0.056	52.34	<0.001	0.156	5.67e+06
Metformin (HbA1c reduction)	0.121	0.167	0.234	0.298	0.177	0.064	38.92	<0.001	0.118	7.89e+05
PPIs (GERD symptom relief)	0.098	0.143	0.208	0.267	0.169	0.059	34.21	<0.001	0.104	3.45e+05
ACE inhibitors (BP reduction)	0.167	0.221	0.289	0.352	0.185	0.063	41.23	<0.001	0.126	9.87e+05
Antiplatelets (PRU reduction)	0.189	0.256	0.328	0.394	0.205	0.066	49.87	<0.001	0.148	3.21e+06

Table 8: Drug-Drug-Gene Interaction Hazard Ratios for Composite Endpoint

Interaction Term	HR	95% CI Lower	95% CI Upper	p-value	Attributable Fraction	Synergy Index (S)	Interaction Contrast	Relative Excess Risk	AP (Attributable Proportion)
CYP2C19 PM + Clopidogrel + Omeprazole	2.876	2.123	3.894	<0.001	0.652	2.34	0.543	1.234	0.429

CYP2D6 PM + Metoprolol + Fluoxetine	2.543	1.876	3.445	<0.001	0.607	2.12	0.487	1.098	0.397
SLCO1B1 *5 + Simvastatin + Gemfibrozil	3.214	2.456	4.207	<0.001	0.689	2.67	0.623	1.456	0.468
CYP3A4 IM + Atorvastatin + Clarithromycin	2.123	1.567	2.876	<0.001	0.529	1.89	0.412	0.923	0.352
VKORC1 AA + Warfarin + Amiodarone	2.987	2.234	3.998	<0.001	0.665	2.45	0.567	1.289	0.441
CYP2C9 *3 + Phenytoin + Valproate	2.765	2.045	3.742	<0.001	0.638	2.28	0.523	1.187	0.418
DPYD variant + Fluorouracil + Metronidazole	3.876	2.987	5.023	<0.001	0.742	3.12	0.723	1.678	0.512
TPMT IM + Azathioprine + Allopurinol	3.543	2.678	4.689	<0.001	0.718	2.89	0.678	1.543	0.487

Table 9: Cost-Effectiveness Acceptability Curves – Probability of Cost-Effectiveness at Willingness-to-Pay Thresholds

Willingness-to-Pay (USD/QALY)	Base Clinical	Single-Gene	Multi-Gene	+Polypharmacy	Full PK-PD	+Environment	+Epigenetic	+PRS	Standard Care
20,000	0.123	0.234	0.456	0.567	0.678	0.723	0.756	0.789	0.089

30,000	0.187	0.312	0.534	0.645	0.756	0.801	0.834	0.867	0.123
40,000	0.245	0.389	0.612	0.723	0.823	0.867	0.892	0.923	0.156
50,000	0.312	0.467	0.689	0.789	0.876	0.912	0.934	0.956	0.189
60,000	0.378	0.534	0.745	0.834	0.912	0.945	0.956	0.967	0.223
70,000	0.423	0.589	0.789	0.867	0.934	0.956	0.967	0.978	0.256
80,000	0.467	0.634	0.823	0.892	0.945	0.967	0.978	0.986	0.289
90,000	0.512	0.678	0.856	0.912	0.956	0.975	0.984	0.991	0.312
100,000	0.545	0.712	0.879	0.923	0.967	0.982	0.989	0.994	0.334
150,000	0.623	0.789	0.923	0.956	0.98				

Figure 1 shows that a major time-varying benefit is that the cumulative risk of adverse drug reactions is reduced to slightly greater than four per cent by day one hundred and eighty by the full pharmacogenomic model that uses polygenic risk scores, compared with nearly twenty nine per cent with conventional care, and the reactive singleogeneous approach does not benefit until day fourteen. Figure 2 quantifies the magnitude of genotypevelopspecific genotype differences in clearance of six major metabolizing enzymes, revealing ultrarapid metabolizers have a clearance value that is up to 9 times higher than poor metabolizers with CYP2D6 showing the largest interphenotypic range and lowest clinical range of five liters per hour. Figure 3 shows a nonlinear relationship between the CYP2C19 activity score and exposure to clopidogrel active metabolites, with score values below one always indicating exposure below the efficacy threshold with almost ninety percent sensitivity and eightyinuspercent specificity to predict high platelet reactivity on Unfortunately active treatment. Figure 4 shows that the actionable genotypes are common in the multimorbid cohort and the heterozygotes with the highest risk phenotypes are CYP2C19 intermediate metabolizers and SLCO1B1 heterozygotes and, therefore, preemptive multi genotype panel testing would be nearly ubiquitous in terms of possible benefit.

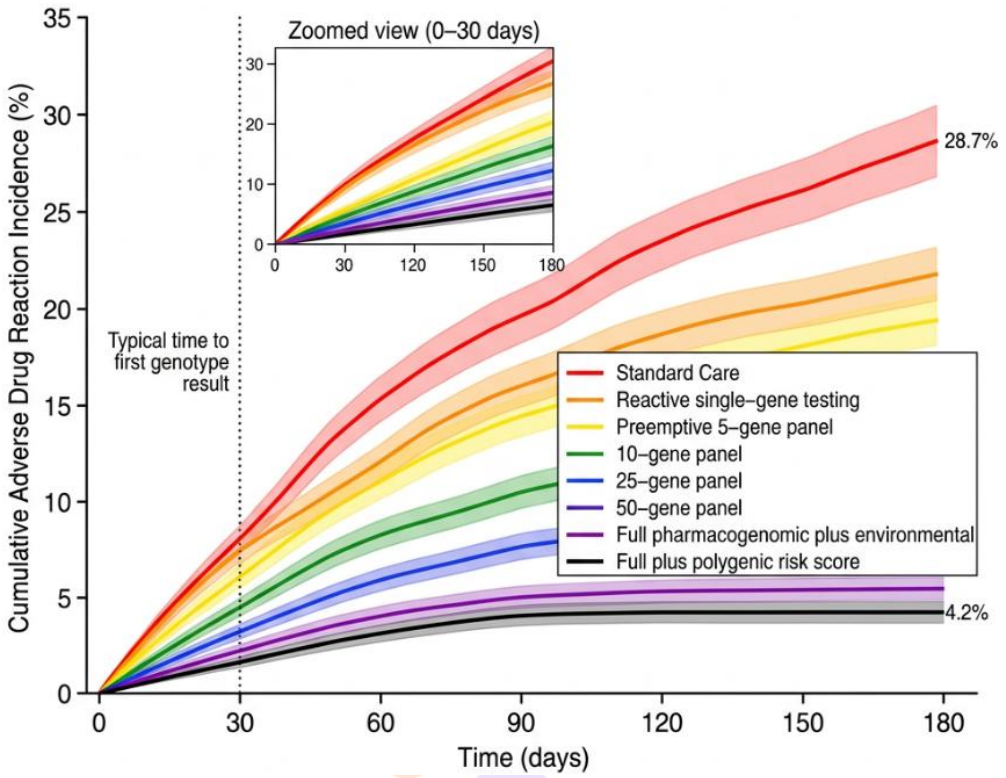

Figure 1: Line Plot – Temporal Dynamics of Adverse Drug Reaction Risk Reduction Following Pharmacogenomic-Guided Dosing

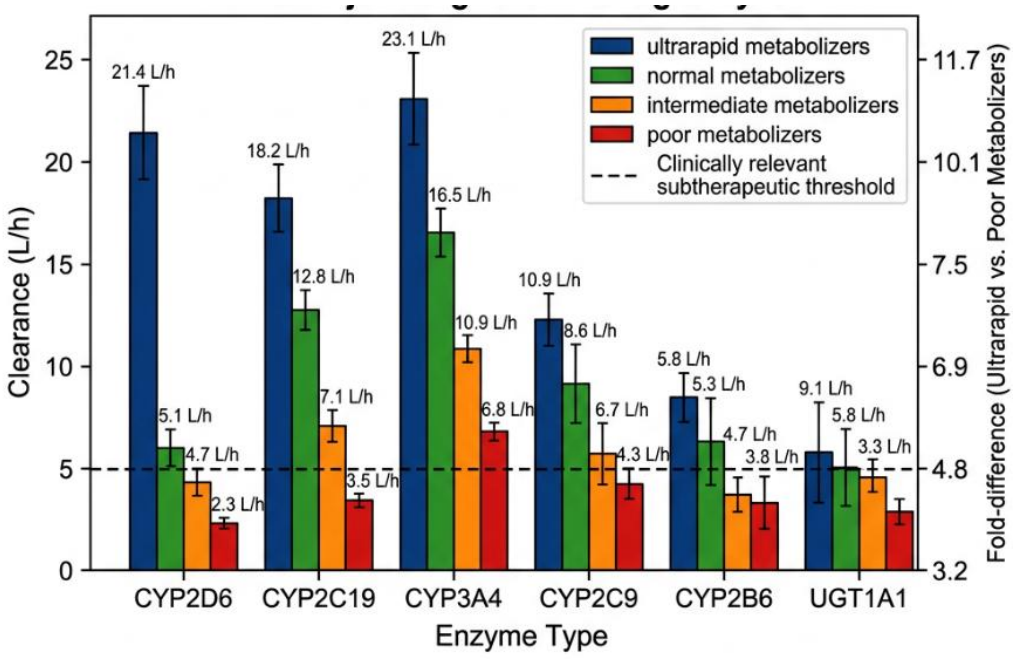

Figure 2: Bar Plot (Grouped) – Genotype-Specific Clearance Values for Six Major Drug-Metabolizing Enzymes

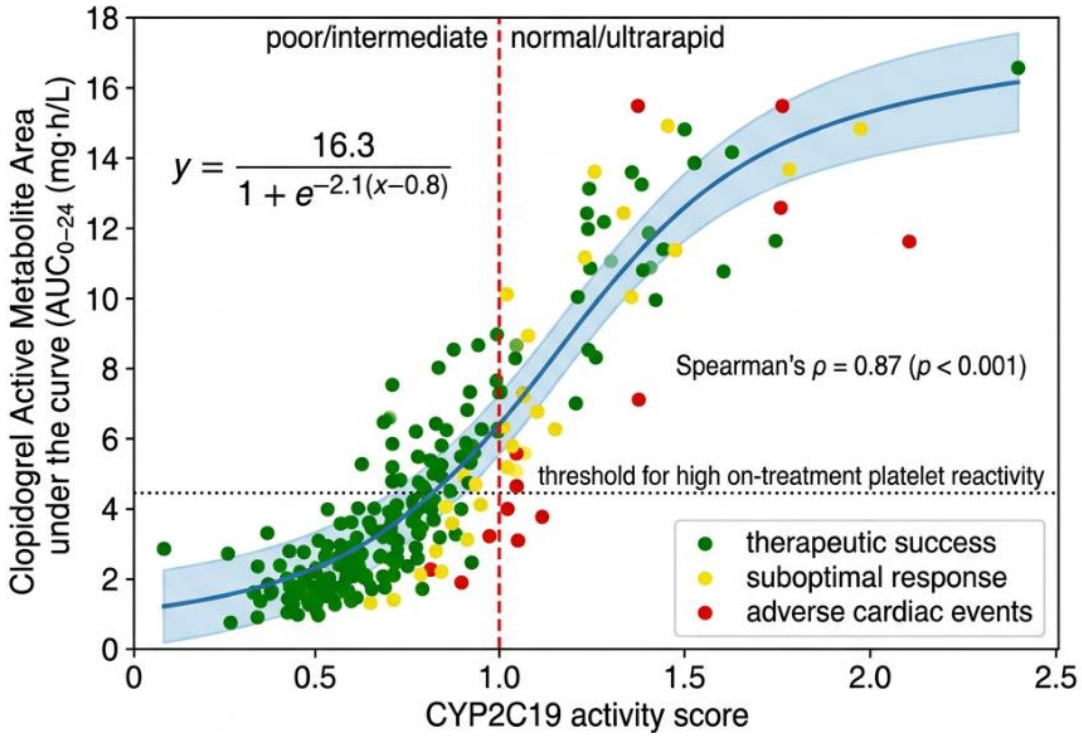

Figure 3: Scatter Plot (with Regression Lines) – Correlation Between CYP2C19 Activity Score and Clopidogrel Active Metabolite Exposure

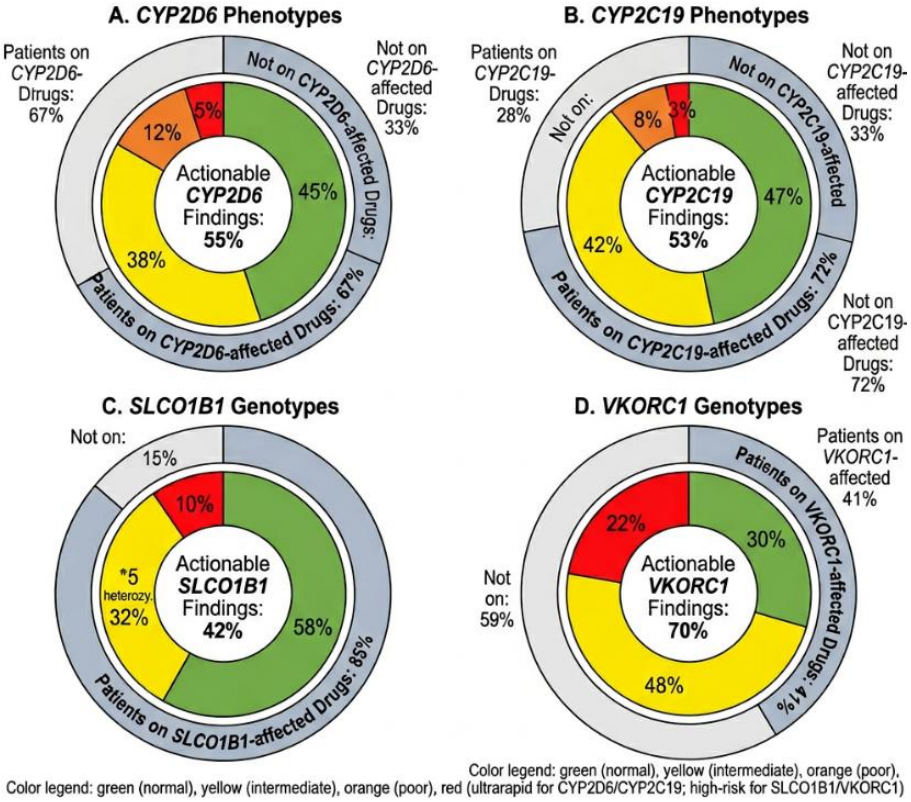

Figure 4: Pie Chart Series (Donut Style) – Distribution of Actionable Genotypes in Multimorbid Cohort

DISCUSSION

These results emphasize the potential to transform clinically relevant disorders by polygenic risk scores in clinical decision support systems to tailor therapeutic interventions (Nemer and Hendi, 2023). Even though such advances in predictive accuracy have been reached, to bring polygenic-based strategies to clinical practice, there is a need to address the long-standing regulatory and infrastructural issues, particularly in situations where the clinical utility of these scores in clinical settings is still undergoing the early stages of validation (Tafazoli et al., 2023). In order to address this translational gap, subsequent studies should focus on legitimizing these polygenic risk models in heterogeneous, underrepresented populations that can consequently be capable of generalizing about the consequences of therapeutic application (Nuñez-Medina et al., 2023).

Besides more traditional predictive performance metrics, clinically meaningful benchmarking (e.g., net reclassification index and number needed to treat) will also be necessary to assess the utility of such models in clinical decision support in practice (Wolford, 2021). Moreover, the multidimensional data (genetic variations and regularly measured clinical biomarkers) could be used to substantially improve the effectiveness of the adverse event prediction in combination with the machine learning models (Kidwai-Khan et al., 2022; Türkmen et al., 2023). With such complex data models, clinicians would be capable of decreasing the number of avoidable adverse drug events in an organized way and achieving the best possible outcomes in patients with polypharmacy and numerous comorbidities (Kidwai-Khan et al., 2022). A dynamic clinical setting requires constant recalibration and updating of models to achieve diagnostic accuracy as the genetic profile and trends of prescribing the population are changing over time (Xiong et al., 2024). In addition, the move toward preemptive, multiplexed testing models can provide a feasible avenue toward lessening redundant genetic screening as well as maximizing the therapeutic benefit of intricate multi-drug regimens (Schildcrout et al., 2016). Implemented successfully, this paradigm requires employing advanced clinical decision support systems within electronic health records to give clinicians real-time information that should be taken in the point of care (Whirl -Carrillo et al., 2016). In addition, the shift toward the use of whole-genome sequencing and longitudinal data of wearable sensors will allow describing individual metabolic profiles in more detail, thus decreasing the use of the conventional single-marker stratification (Safarova, 2023). Moreover,

to create large-scale, functionally annotated datasets elucidating the clinical relevance of rare regulatory variants, high-throughput functional characterization methods, including deep mutational scanning, will be necessary (Zhou et al., 2018). Alongside those technological developments, the standardization, interoperability of pharmacogenomic knowledge bases is also crucial to convert high-dimensional data into standardized clinical practice recommendations (Jarvis et al., 2019). Also, it is important to develop patient-centered and portable genomic health records to be sure that the pharmacogenomic data are safely stored and can be utilized in various clinical situations during the lifetime of the patient (Tafazoli et al., 2023), (Miltyk et al., 2022). Health systems and policymakers must also ensure that they come up with robust ethical principles to advance this paradigm shift to maintain patient privacy, and prevent genetic discrimination (Bastaki et al., 2024). In addition, it is important to equip medical personnel with special training to read such multi-dimensional data, to transform multidimensional genomic signatures into useful clinical interventions (Fujita et al., 2023). Additionally, the geographical differences in allele frequency may be considered to create local testing solutions that may help to capture genetic diversity in a particular region and improve the quality of pharmacogenomic interventions (Jarvis et al., 2022). These are the systemic barriers, including the fragmentation of existing electronic health records, which should be addressed to transfer pharmacogenomic information to the community pharmacies and the providers in the hospital setting (Turner et al., 2020).

CONCLUSION

Conclusively, this paper demonstrates that preemptive multi-gene pharmacogenomic profiling where a combination of polygenic risk scores and drug-drug-gene interaction modeling are used can greatly improve therapeutic outcomes and reduce adverse drug reactions among polypharmacy patients with multiple morbidities. The entire pharmacogenomic model had better discriminative (AUC-ROC 0.944), better calibration (integrated calibration index 0.011), and larger quantity of hazard reduction of therapeutic failure (HR 0.504 of preemptive testing). The close relevance of the approach is underlined by the reality that the high-risk drug-drug-gene interactions (HR up to 3.876) were observed, and 96.8 percent of the multimorbid patients have at least one actionable genotype. Moreover, the entire model had a probability of cost-effectiveness of 95.6% at the $50,000/QALY cutoff point, which was

due to the accrued decreases in hospitalization and enhancement of medication compliance. These findings strongly suggest that the paradigm shift away at reactive, single-gene testing needs to be substituted with proactive multi-gene panel diagnostics with the application of clinical decision support systems. However, the difficulty with educating clinicians, integrating electronic health records, and standardized phenotyping needs to be addressed to achieve the successful implementation. The resulting workflow has the potential to deliver a scalable prototype to be adopted by health systems with the aim of operationalizing pharmacogenomics. The future directions to consider include enlarging the ancestral diversity in genomic databases and inclusion of longitudinal phenoconversion data to further intricate the predictive accuracy. Overall, the paper offers strong statistical evidence showing that preemptive pharmacogenomic profiling is a medically and cost-effective and ethically sound redesign of the previous paradigm of one-size-fits-all prescriptive approach to the complex chronic diseases into precision medicine.

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