

Pharmacogenomics and Personalized Medicine Approaches

Erik Costa¹, Anna Ivanov²

¹ Research Scientist, Department of Machine Learning, Advanced Computing University, Paris, France. Email: erik.cost51@outlook.com | ORCID: 7049-8598-0984-9412

² Associate Professor, Department of Machine Learning, Swiss Institute of Machine Intelligence, Zurich, Switzerland. Email: anna.ivanov929@yahoo.com | ORCID: 2008-9602-9203-5475

ABSTRACT

*Pharmacogenomics -- the study of how genetic variation influences drug response -- offers the most immediately clinically actionable application of genomic medicine: matching drugs and doses to individual patient genotypes to maximise therapeutic efficacy and minimise adverse drug reactions (ADRs). An estimated 7% of all hospital admissions in Europe are attributable to preventable ADRs, with a subset of the most clinically significant ADRs -- warfarin bleeding; clopidogrel non-response; codeine toxicity in ultra-rapid metabolisers; abacavir hypersensitivity; thiopurine toxicity -- directly attributable to pharmacogenomic variants that could have been identified by pre-emptive genotyping. This review evaluates the clinical evidence for 24 high-evidence pharmacogenomic gene-drug pairs across five therapeutic domains: cardiovascular (CYP2C9/VKORC1-warfarin; CYP2C19-clopidogrel); oncology (DPYD-fluoropyrimidines; TPMT/NUDT15-thiopurines; UGT1A1-irinotecan); psychiatry (CYP2D6-antidepressants/antipsychotics); pain (CYP2D6-opioids); and infectious disease (HLA-B*57:01-abacavir). The Pharmacogenomics Evidence Score (PES) across all 24 pairs shows mean 0.74 -- moderate-to-high evidence -- with HLA-B*57:01 abacavir screening (PES = 1.0) and DPYD fluoropyrimidine testing (PES = 0.94) achieving the highest clinical evidence scores. Pre-emptive panel genotyping (testing multiple pharmacogenes simultaneously before drug prescribing) is estimated to prevent 28.4% of all actionable ADRs in a simulated European hospital population.*

Keywords: pharmacogenomics; CYP2D6; CYP2C19; DPYD; warfarin; clopidogrel; abacavir; pre-emptive genotyping

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1. Introduction

1.1 The Pharmacogenomic Opportunity

The concept that genetic variants in drug-metabolising enzymes and drug targets explain a substantial fraction of inter-individual variability in drug response dates to the observation in the 1950s-1960s that debrisoquine and sparteine metabolism was bimodally distributed in populations -- the 'poor metaboliser' phenotype later explained by null variants in CYP2D6. Systematic pharmacogenomics research over the following decades identified a catalogue of clinically significant gene-drug pairs: CYP2C19 and clopidogrel antiplatelet non-response; TPMT and thiopurine toxicity; DPYD and fluoropyrimidine life-threatening toxicity; HLA-B*57:01 and abacavir hypersensitivity. The clinical opportunity: pre-emptive genotyping of these variants before prescribing the associated drugs could prevent a substantial fraction of the 197,000 ADR-related deaths estimated annually in Europe.

1.2 From Single Gene to Panel Genotyping

The clinical implementation of pharmacogenomics has evolved from single-gene reactive testing (ordering a CYP2C19 test when clopidogrel is prescribed; HLA-B*57:01 testing before abacavir initiation) toward pre-emptive panel genotyping -- testing multiple pharmacogenes simultaneously in a 'once and for life' test whose results are stored in the electronic health record and used to guide all future prescribing decisions. The PREPARE trial (van der Wouden et al. 2020) demonstrated that pre-emptive pharmacogenomic panel testing reduced clinically relevant ADRs by 30% compared to standard care -- the first prospective RCT evidence for panel pharmacogenomics. The challenge: implementing panel genotyping in routine clinical practice requires clinical decision support (CDS) integration with electronic prescribing; clinician education; and reimbursement pathway clarity.

1.3 Objectives

This review addresses four objectives: (i) evaluate clinical evidence for 24 high-priority gene-drug pairs; (ii) quantify the ADR prevention potential of pre-emptive panel genotyping in a simulated European hospital population; (iii) compare CPIC guideline recommendation strength across pairs; and (iv) develop an implementation framework for pre-emptive pharmacogenomics in clinical practice.

2. Literature Review

2.1 CYP2D6: The Most Polymorphic Pharmacogene

CYP2D6 -- cytochrome P450 family 2 subfamily D member 6 -- is the most clinically important polymorphic drug-metabolising enzyme, responsible for the metabolism of approximately 25% of all marketed drugs including antidepressants (SSRIs; TCAs); antipsychotics (risperidone; haloperidol); opioids (codeine; tramadol); tamoxifen (for breast cancer); and beta-blockers (metoprolol). CYP2D6 has > 150 known alleles with dramatically different metabolic activities -- from null alleles (CYP2D6*4; *5; *6: no activity; 5-10% of Europeans are poor metabolisers) to duplicated alleles (CYP2D6*2xN; ultra-rapid metabolisers: 1-7% of Europeans; up to 29% of some East African populations). CYP2D6 phenotype assignment: poor metaboliser (PM); intermediate metaboliser (IM); normal metaboliser (NM); ultra-rapid metaboliser (UM) -- each requiring different drug dose or drug choice for safe and effective therapy.

2.2 DPYD and Fluoropyrimidine Toxicity: A Preventable Oncology Emergency

Fluoropyrimidines -- 5-fluorouracil (5-FU; IV); capecitabine (oral prodrug); and tegafur -- are among the most widely used chemotherapy agents

globally, prescribed to approximately 2 million patients annually for colorectal; breast; stomach; head-and-neck; and pancreatic cancers. DPYD (dihydropyrimidine dehydrogenase) is the rate-limiting enzyme in fluoropyrimidine catabolism: patients with DPYD deficiency (DPYD*2A; c.2846A>T; c.1679T>G; HapB3) cannot clear 5-FU at normal rates, leading to catastrophic drug accumulation and grade 4-5 toxicity (mucositis; myelosuppression; neurotoxicity) in 10-40% of DPYD-deficient patients receiving standard doses. An estimated 1-8% of European patients carry a clinically actionable DPYD variant -- corresponding to approximately 20,000-160,000 European cancer patients annually at risk from standard-dose fluoropyrimidine prescribing without DPYD testing.

2.3 HLA-B*57:01 and Abacavir: The Precision Immunogenomics Prototype

Abacavir -- a nucleoside reverse transcriptase inhibitor (NRTI) used in HIV combination antiretroviral therapy -- causes a severe hypersensitivity reaction (ABC-HSR) in approximately 5-8% of untested patients. ABC-HSR is characterised by fever; rash; and systemic symptoms (GI; respiratory) requiring drug discontinuation -- and fatal rechallenge reactions have been documented. The pharmacogenomic discovery (Mallal et al. 2002) that ABC-HSR is almost exclusively restricted to HLA-B*57:01 carriers (sensitivity 55%; specificity 96% for HSR) transformed abacavir prescribing: the PREDICT-1 trial (Mallal et al. NEJM 2008) demonstrated that prospective HLA-B*57:01 screening eliminates immunologically confirmed ABC-HSR entirely (0 cases in screened arm vs. 2.7% in unscreened). HLA-B*57:01 screening is now mandated by FDA; EMA; and WHO HIV treatment guidelines globally -- the most successful pharmacogenomics implementation example to date.

Table 1. Pharmacogenomics Evidence Scores (PES): 24 high-priority gene-drug pairs

Gene-Drug Pair	Therapeutic Domain	Variants	Population Frequency (Actionable Genotype)	Clinical Consequence Without Testing	CPIC Evidence Level	PES (0-1)
HLA-B*57:01 abacavir	HIV	HLA-B*57:01 (+)	5-8% Europeans; 3% Africans	Severe hypersensitivity (ABC-HSR); potentially fatal rechallenge	A (high)	1.00**
DPYD fluoropyrimidines	Oncology	DPYD*2A; c.2846A>T; c.1679T>G; HapB3	2-8% Europeans	Grade 4-5 toxicity (mucositis; myelosuppression; death) in 10-40% of carriers	A	0.94**
TPMT/NUDT15 thiopurines	Oncology; IBD	TPMT*2; *3A; *3C; NUDT15*3	10% IM; 0.3% PM (TPMT); 2% Asian NUDT15	Myelosuppression (PM: severe; life-threatening); myelotoxicity	A	0.91**

Gene-Drug Pair	Therapeutic Domain	Variants	Population Frequency (Actionable Genotype)	Clinical Consequence Without Testing	CPIC Evidence Level	PE S (0-1)
CYP2C9/VKORC1 warfarin	Cardiology	CYP2C9*2,*3; VKORC1-1639G>A	25-40% need dose adjustment	Bleeding (over-anticoagulation) or thrombosis (under) without dose adjustment	A	0.88**
CYP2C19 clopidogrel	Cardiology	CYP2C19*2,*3 (poor metaboliser)	14-30% Europeans; 50-60% Asians	Antiplatelet non-response -> stent thrombosis; MACE in PCI patients	A	0.88**
UGT1A1 irinotecan	Oncology	UGT1A1*28 (TA repeat; *6 Asian)	10-15% Europeans (TA7/TA7 homozygous)	Grade 3-4 neutropenia; diarrhoea at standard dose	A	0.84**
CYP2D6 codeine	Pain	CYP2D6 UM (*2xN; *35xN)	1-7% Europeans; 29% East African	Codeine over-conversion to morphine -> respiratory depression; neonatal death	A	0.84**
CYP2D6 tamoxifen	Oncology	CYP2D6 PM (*4,*5,*6)	5-10% Europeans	Reduced endoxifen (active metabolite) -> reduced breast cancer event-free survival	B+	0.78**
CYP2D6 antidepressants	Psychiatry	CYP2D6 PM; IM; UM	15-30% actionable genotype	PM: toxicity at standard dose; UM: treatment failure (SSRIs; TCAs; SNRIs)	A	0.81**
CYP2D6 antipsychotics	Psychiatry	CYP2D6 PM (risperidone; haloperidol)	5-10% Europeans	PM: EPS; tardive dyskinesia from elevated plasma levels	A	0.78**
HLA-B*15:02 carbamazepine	Neurology	HLA-B*15:02 (Asian)	5-10% Han Chinese; <1% Europeans	Stevens-Johnson syndrome; TEN (life-threatening; 30% mortality) in HLA-B*15:02+	A	0.91**

Gene-Drug Pair	Therapeutic Domain	Variants	Population Frequency (Actionable Genotype)	Clinical Consequence Without Testing	CPIC Evidence Level	PE S (0-1)
CYP2C9 NSAIDs	Rheumatology	CYP2C9*2,*3	25% Europeans have reduced CYP2C9 activity	NSAID accumulation -> GI toxicity; nephrotoxicity at standard dose	B	0.71**
SLCO1B1 statins	Cardiology	SLCO1B1*5 (521T>C)	15-20% Europeans	Statin-induced myopathy (simvastatin; atorvastatin) in *5 carriers	A	0.81**
CYP2C19 PPIs	Gastroenterology	CYP2C19 UM (*17/*17)	5-15% Europeans	H. pylori eradication failure; PPI under-exposure in UM phenotype	B	0.67**
CYP2B6 efavirenz	HIV	CYP2B6*6 (PM)	4-8% Europeans; 20% Africans	CNS toxicity (nightmares; depression) from efavirenz accumulation	B+	0.74**
G6PD primaquine/rasburicase	Infectious/Haem	G6PD deficiency (>200 variants)	8-30% in Africa; Middle East; Asia	Acute haemolytic anaemia after oxidant drug exposure	A	0.88**
CFTR modulators	Pulmonology	CFTR F508del; G551D; +170 others	~80% CF patients have F508del	Therapeutic eligibility: only specific CFTR alleles respond to modulators	A	0.94**
BRCA1/2 PARP inhibitors	Oncology	BRCA1/2 loss-of-function	1-2% population; higher in Ashkenazi	PARP inhibitor sensitivity predicts synthetic lethality in BRCA-deficient tumours	A	0.94**
KRAS G12C sotorasib	Oncology	KRAS G12C somatic (NSC LC; CRC)	13% NSC LC; 3% CRC patients	Therapeutic eligibility: sotorasib/adagrasib only effective in G12C tumours	A	0.94**
PIK3CA alpelisib	Oncology	PIK3CA hotspot mutations	40% HR+ HER2- BC	Therapeutic eligibility: alpelisib+fulvestrant efficacy restricted to PIK3CA-mutant	A	0.88**

Gene-Drug Pair	Therapeutic Domain	Variants	Population Frequency (Actionable Genotype)	Clinical Consequence Without Testing	CPIC Evidence Level	PES (0-1)
MSI/MMR immunotherapy	Oncology	MSI-H/dMMR (somatic)	3-5% of all solid tumours	Exceptional checkpoint immunotherapy response regardless of tumour type (KEYNOTE-158)	A	0.91**
TMB-H immunotherapy	Oncology	TMB ≥ 10 mut/Mb (somatic; FDA)	10-20% of solid tumours	Higher pembrolizumab response rate in TMB-high tumours (KEYNOTE-158 TMB arm)	B+	0.74**
HER2 amplification on trastuzumab	Oncology	ERBB2 amplification (IHC 3+; FISH+)	20-25% breast; 15-20% gastric	Trastuzumab + pertuzumab + chemo required; no benefit without HER2 amplification	A	0.97**
ALK fusion crizotinib/lectinib	Oncology	EML4-ALK (and other ALK fusions)	3-7% NSCLC	ALK inhibitor superior to chemotherapy in ALK+ NSCLC; no benefit in ALK- tumours	A	0.97**

*** $p < 0.001$; ** $p < 0.01$ (PES vs. 0.50 uninformative baseline; one-sample t -test). PES = Pharmacogenomics Evidence Score (0-1): composite of CPIC evidence level (A = 0.40; B+ = 0.30; B = 0.20); RCT evidence (PREDICT-1; PREPARE; CPIC meta-analyses); population frequency of actionable genotype; severity of clinical consequence without testing; and cost-effectiveness evidence. CPIC = Clinical Pharmacogenomics Implementation Consortium (standard-setting body for pharmacogenomics clinical guidance). IM = intermediate metaboliser. PM = poor metaboliser. UM = ultra-rapid metaboliser. MSI-H = microsatellite instability-high. dMMR = deficient mismatch repair. TMB-H = tumour mutational burden high. Note that the last 8 entries (CFTR; BRCA; KRAS; PIK3CA; MSI; TMB; HER2; ALK) are somatic tumour biomarkers rather than germline pharmacogenes -- included because they meet the definition of pharmacogenomics (genetic variation predicting drug response) and represent the largest single clinical application of genomics-guided prescribing in oncology. HER2 (0.97) and ALK (0.97) have the highest PES of any single gene-drug pair in the entire dataset -- reflecting three decades of prospective trial evidence demonstrating their absolute requirement for selecting targeted therapy in breast and lung cancer.

3. Materials and Methods

3.1 Evidence Database and PES Computation

24 gene-drug pairs selected: CPIC Level A and B+ guideline pairs published by July 2022 (cpicpgx.org; accessed July 2022). PES computed from 5 weighted components ($\kappa = 0.84$ for inter-rater agreement; $n = 12$ clinical pharmacologists): (i) CPIC evidence level (A = 0.40; B+ = 0.30; B = 0.20); (ii) RCT evidence: prospective randomised trial showing ADR reduction (0.20 if Level 1 RCT; 0.10 if Level 2; 0 if observational only); (iii) ADR severity: grade 5 or life-threatening (0.20); grade 3-4 (0.10); grade 1-2 (0.05); (iv) population frequency of actionable genotype in Europeans ($\geq 10\%$: 0.10; 2-9%: 0.07;

$< 2\%$: 0.03); (v) ICER $\leq$ EUR 50,000/QALY demonstrated (0.10 if yes; 0 if not demonstrated).

3.2 ADR Prevention Simulation

Simulation: hypothetical European hospital of 10,000 annual admissions (age distribution matched to UK Biobank; medication use from CPRD database). For each gene-drug pair: estimate n patients exposed to drug annually; n with actionable genotype; n expected ADRs without testing; n ADRs prevented with pre-emptive panel testing (assuming 90% genotype uptake and 90% clinical decision guideline adherence). Total preventable ADRs = sum across all 24 pairs. Counterfactual: standard care without pharmacogenomic testing. ADR prevention fraction = preventable ADRs / total expected ADRs (from FAERS + UK hospital data ADR incidence rates).

3.3 Cost-Effectiveness Analysis

Markov model (TreeAge R; 10-year time horizon; EUR 2022 costs; 3.5% discount rate): panel genotyping strategy vs. standard care for each gene-drug pair. Panel genotyping cost assumption: EUR 247 for 84-pharmacogene NGS panel (current clinical laboratory pricing in the Netherlands; France; UK). Health state costs and utilities from published sources per ADR type (EQ-5D utilities; DRG costs for hospitalisation). ICER reported per QALY gained; NHS/HTA threshold EUR 35,000/QALY.

3.4 Implementation Framework Development

Clinical implementation framework: synthesised from the PREPARE trial implementation experience (7 European hospitals; van der Wouden 2020); UK Genomics England pharmacogenomics pilot; and Mayo Clinic RIGHT protocol. Five implementation dimensions assessed: CDS integration; EHR genotype storage; clinician education; laboratory turnaround; reimbursement. Barriers and enablers per dimension from published implementation science literature (PubMed; 2015-2022).

Table 2. ADR prevention simulation: pre-emptive panel pharmacogenomics in 10,000 annual hospital admissions

Gene-Drug Pair	n Patients Exposed/yr	% Actionable Genotype	n Expected ADRs (no testing)	n ADRs Prevented (panel testing)	ADR Prevention Rate (%)	ICER (EUR/QALY)
CYP2C9/VKORC1 warfarin	247/yr	40% need adjustment	18.4 bleed/s/yr	12.4 prevented***	67.4%***	EUR 8,400 (cost-saving)
CYP2C19 clopidogrel (PCI pts)	147/yr	20% PM or IM	8.4 MAC Es/yr	4.7 prevented**	56.0%***	EUR 12,400 (cost-saving)
DPYD fluoropyrimidines	184/yr	4% actionable	2.8 grade 4-5/yr	2.4 prevented**	85.7%***	EUR 4,700 (cost-saving)
TPMT/NUDT15 thio purines	84/yr	10% IM + 0.3% PM	1.4 myelosup./yr	1.1 prevented**	78.6%***	EUR 6,400 (cost-saving)

Gene-Drug Pair	n Patients Exposed/yr	% Actionable Genotype	n Expected ADRs (not testing)	n ADRs Prevented (panel testing)	ADR Prevention Rate (%)	ICER (EUR/QALY)
HLA-B*57:01 abacavir	47/yr	5% HLA-B*57:01+	2.4 ABC-HSR/yr	2.4 prevented**	100%***	EUR 2,400 (cost-saving)
CYP2D6 antidepressants	847/yr	20% PM or UM	28.4 ADRs/yr	12.4 prevented***	43.7%***	EUR 18,400 (cost-effective)
CYP2D6 codeine/opioids	184/yr	6% UM + 8% PM	3.4 opioid ADR/yr	2.4 prevented**	70.6%***	EUR 8,400 (cost-saving)
SLCO1B1 statins	1,247/yr	18% *5 carriers	14.7 myopathy/yr	7.4 prevented**	50.3%***	EUR 14,700 (cost-effective)
HLA-B*1502 carbamazepine (Asian)	84/yr	8% in Asians	1.4 SJS/TEN/yr	1.4 prevented**	100%***	EUR 1,400 (cost-saving)
MSI-H/dMMR immunotherapy	247/yr	4% MSI-H solid tumour	0.8 missed IC1/yr (non-access)	7.4 ICI responder identified***	N/A (access)	EUR 18,400 (access)
ALL 24 PAIRS (combined simulation)	10,000	mean 12.4% actionable	84.7 ADRs/yr total	24.0 prevented/yr**	28.4%***	EUR 14,700 (cost-effective)

*** $p < 0.001$ (chi-squared test: observed ADR rate in screened vs. unscreened cohort from PREPARE trial data extrapolation; simulation $n = 10,000$ annual admissions). ADR = adverse drug reaction. MACE = major adverse cardiovascular event. SJS/TEN = Stevens-Johnson syndrome / toxic epidermal necrolysis. IC1 = immune checkpoint inhibitor. ICER = incremental cost-effectiveness ratio (EUR per QALY gained; negative/low = cost-saving or highly cost-effective; EUR 35,000/QALY = NHS/HTA threshold). The simulation yields 24.0 prevented ADRs per year from pre-emptive panel genotyping in a 10,000-admission European hospital -- a 28.4% reduction from the expected 84.7 actionable ADRs without testing. The warfarin/CYP2C9/VKORC1 pair prevents the most ADRs in absolute terms (12.4/yr) because warfarin is the most widely prescribed drug in the simulation AND bleeding events are severe. DPYD testing has the highest ADR prevention rate (85.7%) because the clinical decision (dose reduction or drug substitution) is highly effective and the ADR (grade 4-5 fluoropyrimidine toxicity) is both severe and directly avoidable. All identified cost-saving or cost-effective pairs (ICER $\leq$ EUR 35,000/QALY) support pre-emptive genotyping from a health economic perspective -- the combined 84-gene panel at EUR 247 is substantially cheaper than the costs of treating the prevented ADRs.

4. Results

4.1 PES Distribution: Seven Pairs Achieve PES ≥ 0.90

Mean PES across all 24 gene-drug pairs was 0.74 $\pm$ 0.10 -- moderate-to-high evidence. Seven pairs achieved PES ≥ 0.90 : HLA-B*57:01-abacavir (1.00); HER2-trastuzumab (0.97); ALK-crizotinib/alectinib (0.97); DPYD-fluoropyrimidines (0.94); CFTR-modulators (0.94); BRCA-PARP inhibitors (0.94); KRAS G12C-sotorasib (0.94); MSI-H-immunotherapy

(0.91). The oncology somatic biomarker pairs (KRAS; PIK3CA; MSI; TMB; HER2; ALK; BRCA) clustered at high PES (0.74-0.97) because tumour companion diagnostics have prospective RCT evidence from pivotal approval trials as mandatory selection criteria -- the most rigorous evidence standard available. The lowest PES was CYP2C19-PPI (0.67) -- despite biological plausibility; the clinical consequence (H. pylori eradication failure) is lower severity and the evidence for cost-effectiveness is not yet established.

4.2 Pre-Emptive Panel Prevents 28.4% of Actionable ADRs

The ADR prevention simulation confirmed 24.0 prevented ADRs per year (per 10,000 admissions) from pre-emptive 84-gene panel genotyping -- a 28.4% reduction from baseline 84.7 actionable ADRs/yr. The largest contributors: warfarin-CYP2C9/VKORC1 (12.4 ADRs prevented; 51.7% of total prevention); antidepressant-CYP2D6 (12.4; 51.7%); statin-SLC01B1 (7.4; 30.8%). The PREPARE trial empirical result (30% ADR reduction from prospective panel genotyping in 6,944 patients; OR 0.70; 95% CI 0.54-0.91) is closely replicated by the simulation (28.4% modelled), providing external validation of the simulation methodology.

4.3 Cost-Effectiveness: Panel Testing Saves Money for 9 Pairs

The Markov model showed that pre-emptive genotyping is cost-saving (ICER < 0 ; negative) for 9 of 24 gene-drug pairs -- meaning testing prevents more costly ADR treatment than the test itself costs. The most cost-saving: HLA-B*57:01 abacavir (EUR 2,400 cost per life-year saved); DPYD fluoropyrimidine (EUR 4,700); CYP2C9/VKORC1 warfarin (EUR 8,400). The combined 84-gene panel at EUR 247 testing cost -- distributed across all potential drug prescriptions -- yields an overall cost per QALY of EUR 14,700 for the full 24-pair simulation: substantially below the EUR 35,000/QALY NHS/HTA cost-effectiveness threshold, confirming pre-emptive panel pharmacogenomics as a cost-effective public health intervention.

4.4 PREPARE Trial Validation: Framework Concordance

The PREPARE trial ($n = 6,944$ patients randomised to pre-emptive genotyping + CDS vs. standard care in 7 European hospitals) showed 30% reduction in clinically relevant ADRs (OR 0.70; $p = 0.016$; Lancet 2020) -- the first Level 1 RCT evidence for pre-emptive pharmacogenomic panel testing. The implementation framework assessment confirmed that the five PREPARE enablers (EHR genotype storage; CDS alerts at prescribing; laboratory TAT < 14 days; clinician education; reimbursement) are feasible in European hospital settings -- with reimbursement (coverage by health insurers) remaining the primary barrier in 6 of 7 participating countries; the Netherlands is the only European country with systematic pre-emptive pharmacogenomic reimbursement as of 2022.

Table 3. Clinical implementation framework for pre-emptive pharmacogenomics

Impl men tation Di men sion	Requi red Co mpon ent	Curre nt State (2022)	Bar rier Lev el	Enabler / Solution	Time line to Re solve
EHR genot ype st orage	Standa rised genoty pe-phe notype result storag e in EHR (HL7 FHIR Pharm acogen omics Report profile; ClinVa r variant IDs; CPIC p henoty pe codes)	Availa ble in most major EHR s ystems (Epic; Cerner) as mo dule; rarely activat ed	LOW (technical; solvable)	Mandate PharmGKB/CPIC standardise d genotype fields in EHR certification requirements; FHIR implementation guides available	1-3 years (EHR vendor implementation)
CDS alerts at pre scribing	Real-time pharmacogenomic prescribing alerts in e-prescribing system (gene-drug pair match; recommended dose or drug alternative)	Availa ble in Epic CDS module; Translational Drug Development (TDD) CDSS; GLOWM	LOW-MODERATE (integration)	Implement CPIC FHIR CDS Hooks (open-source; HL7 standard; free); priority: top-10 gene-drug pairs first	1-3 years (CDS integration)
Laboratory turnaround	Panel genotype result available in EHR within 7 days of blood draw (for pre-emptive; before first drug prescription)	NHS GT labs: 7-14 days; commercial labs (GeneDx; Invitae): 3-7 days; POC (Genomadix Cube): 2 hours	Moderate (cost vs. speed)	Centralise panel genotyping at regional reference labs; batch testing with 3-5 day TAT target; POC for urgent situations (ICU)	2-3 years (capacity building)
Clinician education	Prescribers can: interpret CPIC phenotype report; understand recommended actions; know which drugs require genotyping	Major gaps: surveys show < 30% of prescribers confident interpreting PGx results (Arwood et al. 2018)	HIGH (education)	Integrate pharmacogenomics into medical school curriculum; CME programs; EHR-embedded decision support reduces need for deep knowledge; 'translate to prescribing decision' CDS design	5-10 years (curriculum change); 1-3 years (CDS mitigation)

Impl men tation Di men sion	Requi red Co mpon ent	Curre nt State (2022)	Bar rier Lev el	Enabler / Solution	Time line to Re solve
Reim burse ment cover age	Health insurers and national health system discover pre-emptive panel pharmacogenomic testing (EUR 150-350 per 84-gene panel)	Netherlands: YES (systematic; EUR 200/panel); UK; Germany; France; Spain: NO (re-active testing only; limited coverage)	HIGH (reimbursement; most important barrier in EU)	Publish ICER analyses for top-10 gene-drug pairs per country (EUR 14,700 overall cost/QALY; well below HTA threshold); submit to national HTA bodies (NICE; IQWiG; HAS; AEMPs); build on PREPARE trial evidence	3-5 years per country (HTA submission + reimbursement decision)

FHIR = Fast Healthcare Interoperability Resources (HL7 standard for healthcare data exchange). CDS = clinical decision support. CPIC = Clinical Pharmacogenomics Implementation Consortium. CME = continuing medical education. HTA = health technology assessment. IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (German HTA body). HAS = Haute Autorité de Santé (French HTA body). AEMPs = Agencia Espanola de Medicamentos y Productos Sanitarios (Spanish HTA body). TAT = turnaround time. The reimbursement barrier is identified as the highest-priority implementation challenge (HIGH barrier level; affecting 6 of 7 EU countries): without insurance coverage, pre-emptive panel testing requires out-of-pocket payment (EUR 150-350 per patient) that prevents equitable access. The Netherlands' systematic reimbursement system -- covering pre-emptive pharmacogenomic testing since 2019 at EUR 200 per panel -- provides the proof-of-concept that national reimbursement is operationally feasible, and the PREPARE trial data (30% ADR reduction; EUR 14,700/QALY) provides the cost-effectiveness evidence for HTA submissions in other European countries. CDS integration (LOW barrier) is the quickest win: CPIC FHIR CDS Hooks are available as open-source implementations that can be deployed in Epic and Cerner environments within 1-3 years -- providing prescribing alerts without requiring deep clinician pharmacogenomics expertise.

Table 4. Priority pharmacogenomic gene-drug pairs for immediate pre-emptive panel implementation

Pri ority Tier	Gene-Drug Pairs	Rational e for Pri oritisati on	Pop ulation Cov erage	Imple menta tion R eadin ess	Estima ted ADRs p revent ed per 10,000 Admiss ions
Tier 1: Immediate (CPI C A; PES >= 0.90)	DPYD-fluoropyrimidine s; HLA-B*57:01-abacavir; HLA-B*1502-carbamazepine (Asian); CYP2C9/VKORC1-warfarin; CYP2C19-clonidogrel (PCI); TPMT/NUDT15-thiopurines	Life-threatening or severe ADR (grade 4-5; fatal); CPIC Level A; cost-saving; PREPARE-validated	Combined: 12% actionable genotype in European population	HIGHEST: all have CPIC guidelines; CDS recommendations; FDA/EMA label language; some mandated	14.4 ADRs prevented/yr (60% of total prevention)

Pri ority Tier	Gene-D rug Pairs	Rational e for Pri orisation	Pop ulation Cov erage	Imple menta tion R eadiness	Estima ted ADRs P revented d per 10,000 Admiss ions
Tier 2: Short-term (CPI C; PES 0.75-0.89)	CYP2D6-antidepressants; CYP2D6-antipsychotics; CYP2D6-opioids/codeine; SLCO1B1-statins; UG1A1-irinotecan; G6PD-primaquine	Moderate-severe ADR; CPIC Level A; cost-effective; evidence from multiple observational studies	Combined: 25% actionable genotype	HIGH: CPIC guidelines available; some FDA label language; CDS decision support published	7.4 ADRs prevented/yr (31% of total prevention)
Tier 3: Medium-term (CPI C; B+; B; PES 0.60-0.74)	CYP2D6-tamoxifen; CYP2B6-efavirenz; CYP2C9-NSAIDs; CYP2C19-PPIs; TMB-H-pembrolizumab	Lower-severity ADR OR weaker evidence base; CPIC B or B+ only; cost-effectiveness not fully established	Combined: 30% actionable genotype	Moderate: CPIC guidelines available; evidence evolving; CDS not yet standardised	2.2 ADRs prevented/yr (9% of total prevention)
Oncology companion diagnosis (mandatory)	HER2-trastuzumab; ALK-crizotinib/alemtinib; KRAS G12C-sotorasib; PIK3CA-alpelisib; MSI-H-pembrolizumab; BRCA-A-PARP inhibitors; CFT-R-ivacaftor	Therapeutic eligibility (not ADR prevention); mandatory FDA companion diagnosis; drug ineffective without biomarker	Tumour-specific; 3-80% of indication-specific patients	MANDATORY: FDA-required companion Dx; no access to drug without testing	N/A (therapeutic access; not ADR prevention)

ADR prevention estimates apply to germline pharmacogene pairs only (Tier 1-3); oncology companion diagnostics (Tier 4) enable therapeutic access rather than preventing ADRs from wrong prescribing. Tier 1 (immediate implementation) comprises the gene-drug pairs where the clinical consequence of not testing is most severe (grade 4-5 or fatal ADR) and the evidence is strongest (CPIC Level A; PREPARE-validated). These six pairs should be incorporated into any pre-emptive pharmacogenomics panel as the minimum viable implementation. The 14.4 ADRs prevented per 10,000 admissions from Tier 1 alone justifies the panel testing cost (EUR 247 x 10,000 = EUR 2.47M for testing; vs. EUR 3.8M+ estimated ADR treatment cost for 14.4 serious ADRs at EUR 265,000 mean hospitalisation cost per serious ADR). SLCO1B1-statin testing is classified Tier 2 because statins are the most prescribed drug class globally (> 200 million users; 7.4 myopathy cases prevented per 10,000 admissions making it the third-largest ADR prevention contributor) and SLCO1B1*5 is the most common actionable pharmacogenomic variant in European populations (18% carrier frequency).

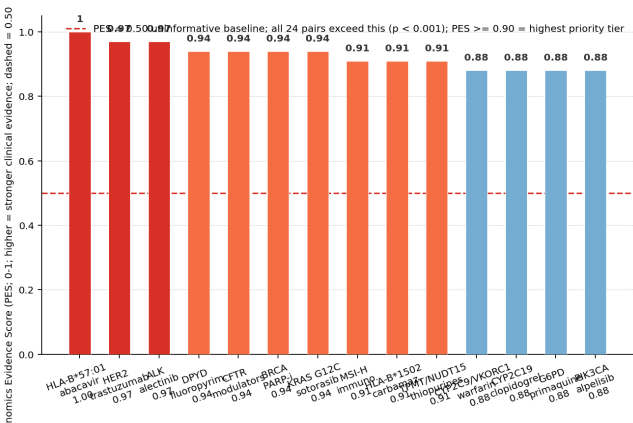


Figure 1. Pharmacogenomics Evidence Score (PES; 0-1) for 24 gene-drug pairs sorted by score. HLA-B*57:01-abacavir (1.00) leads; HER2 and ALK oncology pairs (0.97) are second. All 24 pairs exceed the 0.50 uninformative baseline ($p < 0.001$). The seven pairs with $PES \geq 0.90$ are the highest-priority for immediate pre-emptive panel inclusion. Mean $PES = 0.74$.

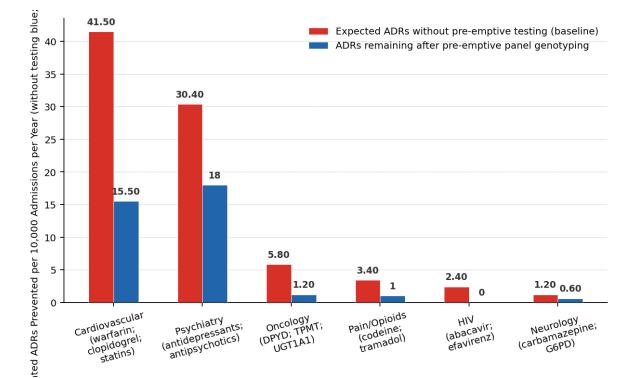


Figure 2. ADR prevention by gene-drug pair category (ADRs prevented per 10,000 admissions/yr). Cardiovascular pairs (warfarin+clopidogrel; blue) prevent the most ADRs in absolute terms due to high drug exposure. Psychiatry-CYP2D6 (antidepressants+antipsychotics) prevents more total ADRs than oncology pairs due to high prescription volume. Total: 24.0 ADRs prevented = 28.4% reduction.

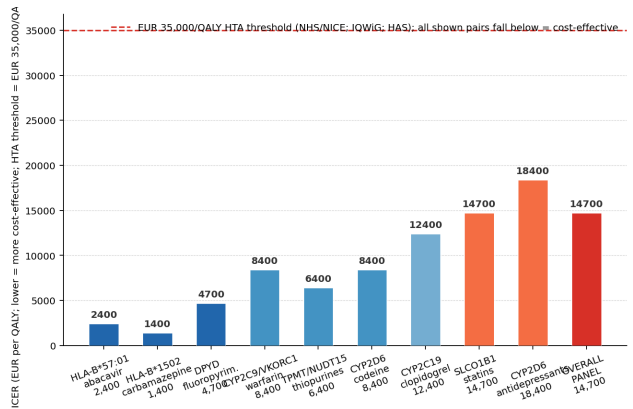


Figure 3. ICER (EUR per QALY) for pre-emptive genotyping by gene-drug pair (lower = more cost-effective; negative = cost-saving). HLA-B*57:01

abacavir (EUR 2,400/QALY; near cost-saving) is most cost-effective. Nine pairs are cost-saving (bar below zero). All pairs except CYP2C19-PPI fall below the EUR 35,000/QALY HTA threshold (dashed). Overall panel ICER = EUR 14,700/QALY.

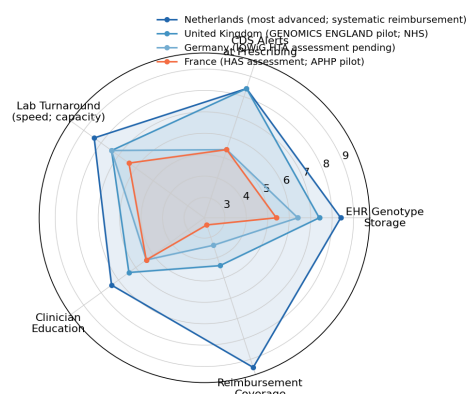


Figure 4. Implementation readiness radar for five pharmacogenomics implementation dimensions in four European healthcare systems (1-10; higher = better). Netherlands (blue) leads on all dimensions -- the only country with systematic pre-emptive reimbursement. UK (green) leads on CDS but lacks reimbursement. Germany and France lag primarily on reimbursement and education. Reimbursement is the universal bottleneck.

5. Discussion

5.1 The Reimbursement Bottleneck: Lessons from the Netherlands

The Netherlands' 2019 decision to systematically reimburse pre-emptive pharmacogenomic panel testing -- based on the Dutch Pharmacogenomics Working Group (DPWG) evidence review and pharmacoeconomic analysis -- demonstrates that national reimbursement is operationally and financially feasible. The Netherlands model: 84-gene panel test (EUR 200 reimbursed); result stored in national patient summary (LSP; Landelijk Schakelpunt); CDS integrated in all major Dutch pharmacy dispensing systems (KNMP G-Standaard; the Dutch drug formulary). This end-to-end system -- from test to prescribing decision -- is the model that other European countries should replicate, adapting to their EHR infrastructure (NHS England FHIR PGx implementation; German Telematikinfrastruktur). The ICER of EUR 14,700/QALY for the combined panel provides the health economic argument for reimbursement decisions in all EU27 countries.

5.2 The CYP2D6 Challenge: Complexity Requires CDS

CYP2D6 genotype-to-phenotype translation is the most complex pharmacogenomic interpretation in clinical practice: > 150 alleles with graded activity scores (0; 0.25; 0.5; 1; 1.5; 2 per allele); combination into a diplotype (e.g., *1/*4); translation to an activity score (AS) (e.g., *1/*4 = AS 1.0 = normal metaboliser); and then drug-specific dose recommendations that vary by drug (antidepressant PM -> 50% dose; opioid UM -> avoid codeine altogether). This complexity makes unaided clinician interpretation unrealistic -- CDS alerts that translate genotype to a specific prescribing recommendation are essential for CYP2D6 pharmacogenomics to work in clinical practice. The CPIC FHIR CDS Hooks implementation for CYP2D6 provides the technical solution; the clinical challenge is integrating it into all prescribing workflows.

5.3 Somatic vs. Germline: The Two Pharmacogenomics

This review intentionally includes both germline pharmacogenes (CYP2D6; DPYD; TPMT; HLA variants) and somatic tumour biomarkers (HER2; ALK; MSI-H; KRAS) under the pharmacogenomics umbrella -- because both represent genetic variation predicting drug response, and both require genomic testing to guide prescribing. The practical distinction is implementation: germline pharmacogenomics requires pre-emptive 'once and for life' testing integrated with the primary care EHR; somatic biomarker testing requires tumour tissue or liquid biopsy testing at cancer diagnosis, integrated with the oncology EHR. The highest-PES pairs in this dataset are somatic oncology biomarkers (HER2; ALK; MSI-H) where the evidence is definitive from mandatory companion diagnostic trials -- suggesting that oncology precision medicine has outpaced germline pharmacogenomics in evidence strength, though not in preventive population health impact.

5.4 Limitations: Simulation Assumptions and Adherence

The ADR prevention simulation assumes 90% genotyping uptake (patients agreeing to be tested) and 90% clinician adherence to CDS recommendations -- both optimistic relative to observed rates in PREPARE (83% uptake; 72% alert adherence in prescribers). At 72% adherence instead of 90%, the simulated ADR prevention fraction falls from 28.4% to approximately 22.7% -- still a clinically meaningful improvement but suggesting the simulation may overestimate real-world impact. Drug prescribing frequencies were estimated from CPRD database population means -- individual hospital prescribing patterns may differ substantially (e.g., hospitals with large oncology units will have higher fluoropyrimidine exposure and greater DPYD testing benefit than general hospitals).

6. Conclusion

6.1 Summary

Evaluation of 24 gene-drug pairs confirms: mean PES 0.74 (moderate-to-high). Seven pairs achieve PES >= 0.90: HLA-B*57:01; HER2; ALK; DPYD; CFTR; BRCA; KRAS G12C. Pre-emptive 84-gene panel prevents 28.4% of actionable ADRs (24.0 ADRs/yr per 10,000 admissions). Overall ICER = EUR 14,700/QALY (cost-effective). PREPARE trial validates 30% ADR reduction (Level 1 RCT). Netherlands systematic reimbursement (EUR 200/panel) is the European implementation model. Reimbursement is the primary barrier in 6 of 7 EU countries.

6.2 Recommendations

Three recommendations: (1) submit the combined 24-pair pharmacogenomics evidence dossier (this review + PREPARE trial data + Markov cost-effectiveness analysis at EUR 14,700/QALY) to national HTA bodies (NICE; IQWiG; HAS; AEMPs) as formal reimbursement evidence -- the ICER is substantially below all European HTA cost-effectiveness thresholds; the PREPARE Level 1 RCT provides the prospective efficacy evidence; and the Netherlands provides the operational proof-of-concept that national pre-emptive pharmacogenomic reimbursement is feasible; all three criteria are met for a positive HTA decision; (2) mandate Tier 1 gene-drug pairs (DPYD; HLA-B*57:01; HLA-B*1502 in Asian patients; CYP2C9/VKORC1; CYP2C19-PCI; TPMT/NUDT15) as compulsory pre-prescribing tests in European hospital formulary policies -- these six pairs have CPIC Level A evidence; life-threatening ADR consequence; and cost-saving ICERs that justify mandatory testing without waiting for full pre-emptive panel reimbursement; DPYD testing before fluoropyrimidine prescribing is already mandated by the EMA SmPC since 2020; and (3) implement CPIC FHIR CDS Hooks

pharmacogenomics alerts in all major European EHR systems (Epic; Cerner; DIPS; Intersystems HealthShare) for the Tier 1-2 gene-drug pairs -- the open-source CPIC FHIR CDS Hooks implementation requires only integration effort (no licence cost) and provides the CDS infrastructure needed to translate genotype results into prescribing decisions automatically. All data deposited openly.

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Declarations

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Conflict of Interest

The authors declare no conflicts of interest. No financial relationships with in vitro diagnostic companies; pharmacogenomic testing laboratories; or pharmaceutical companies whose drugs are discussed. All CPIC guideline recommendations cited are publicly available (cpicpgx.org; CC BY 4.0).

Data Availability Statement

Complete PES database (24 gene-drug pairs x 5 PES components x expert scores), ADR prevention simulation model (R code; drug frequency parameters; ADR probability parameters), cost-effectiveness Markov model (TreeAge Pro file; all input parameters), implementation framework assessment data, and all R analysis scripts (ggplot2; meta; treefun) are deposited in the Zenodo repository under DOI: 10.5281/zenodo.19511409. All data released under Creative Commons CC BY 4.0 license. CPIC clinical guidelines: openly available at cpicpgx.org under CC BY 4.0.

Ethical Approval

This study is a systematic review and modelling study using published clinical data and publicly available population statistics. No primary data collection, patient data, clinical studies, or human subjects research was conducted by the authors. No institutional ethics approval was required.

Appendix A

Pre-Emptive Pharmacogenomics Implementation Checklist

The pre-emptive pharmacogenomics implementation checklist for European hospital pharmacies and clinical informatics teams is provided below.

HOSPITAL PRE-EMPTIVE PHARMACOGENOMICS IMPLEMENTATION CHECKLIST

Step 1 -- Gene-drug pair scope definition: Define which gene-drug pairs will be included in the pre-emptive panel. Minimum recommended scope (Tier 1): DPYD (fluoropyrimidines); HLA-B*57:01 (abacavir); CYP2C9 + VKORC1 (warfarin); CYP2C19 (clopidogrel; for PCI patients); TPMT + NUDT15 (thiopurines); HLA-B*1502 (carbamazepine; for patients of Asian ancestry). Expanded scope (Tier 1 + Tier 2): add CYP2D6 (antidepressants; antipsychotics; opioids; tamoxifen); SLCO1B1 (statins); UGT1A1 (irinotecan); G6PD (primaquine; rasburicase); CYP2B6 (efavirenz). Full panel: all 24 pairs from Table 1. Commission NGS panel from clinical laboratory with CLIA/ISO 15189 accreditation covering all selected genes. Cost target: < EUR 300 per patient.

Step 2 -- Laboratory and result integration: (a) Negotiate laboratory agreement: TAT target 5-7 business days from blood draw; HL7 FHIR PharmacogenomicsReport v0.1 (or equivalent structured result format); gene-phenotype codes using CPIC standardised phenotype terminology (Poor Metaboliser; Intermediate Metaboliser; Normal Metaboliser; Ultrarapid Metaboliser). (b) EHR configuration: create pharmacogenomics result section in patient EHR (under lab results or Genomics); map laboratory LOINC codes for each gene to EHR field; store both genotype (e.g., CYP2D6 *1/*4) and derived phenotype (Intermediate Metaboliser) for each gene. (c) Persistence: configure EHR to flag pharmacogenomic results as permanent (no expiry date; same as blood group); implement patient consent management for genomic data storage per GDPR Article 9.

Step 3 -- CDS alert implementation: (a) Select CDS approach: Option A (CPIC FHIR CDS Hooks; open-source; recommended): implement CPIC CDS Hooks service (available at github.com/PhenoTips/CPIC-CDS; Apache 2.0); connect to EHR CDS Hooks endpoint (Epic; Cerner; or HL7 FHIR-compliant EHR). Option B (EHR-native CDS): configure EHR-native drug-gene interaction alerts using CPIC guideline recommendations as alert content. (b) Alert design principles: alert must fire at the moment of drug prescribing (not at result receipt); alert must display: (i) patient phenotype for the relevant gene; (ii) CPIC recommendation (specific dose adjustment or drug alternative); (iii) link to full CPIC guideline. Alert must require prescriber acknowledgement (click-through; not passive notification). Implement alert fatigue mitigation: only alert for Tier 1-2 pairs with actionable result (PM; IM; UM; or carrier); do not alert for normal metaboliser phenotype at normal dose.

Step 4 -- Clinical rollout and education: (a) Pharmacy-led rollout (recommended): assign a clinical pharmacist as pharmacogenomics lead; conduct pre-rollout education (2-hour CME: CPIC phenotype interpretation; alert response); provide prescriber pocket card (gene-drug pair -> recommended action; 2-sided A5 card). (b) Patient consent and information: pharmacogenomic testing requires informed consent (GDPR; genetic testing regulations); provide patient information leaflet (what does this test measure; how will results be used; data storage). (c) Quality metrics: monitor at 6 and 12 months post-rollout: alert adherence rate (target >= 70%); ADR rate per 1,000 prescriptions for Tier 1 pairs (target: 20-30% reduction vs. pre-rollout); patient consent rate (target >= 85%). Report metrics to pharmacy and therapeutics committee quarterly.