

## Nationwide Implementation of Essential Pharmacogenomic Testing in the Netherlands: A Decision-Analytic Model of Lives Saved and Cost-Effectiveness

Salman Raza<sup>1</sup>, Abdullah Khan<sup>1</sup>, Faisal Mehmood<sup>1\*</sup>, Umar Farooq<sup>1</sup>

<sup>1</sup>Department of Pharmacognosy, Faculty of Pharmacy, University of Punjab, Lahore, Pakistan.

\*E-mail ✉ [faisal.mehmood.pg@gmail.com](mailto:faisal.mehmood.pg@gmail.com)

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### ABSTRACT

Evidence from forward-looking clinical investigations indicates that using pharmacogenomics (PGx) to guide therapy decisions can lower the occurrence of serious and life-threatening drug complications. The Dutch Pharmacogenetics Working Group (DPWG) designates certain drug–gene interaction (DGI) scenarios that can avert drug-associated mortality as “essential,” yet their combined clinical and economic value has not been fully quantified. This study aims to evaluate the national-level impact and cost-effectiveness of applying “essential” PGx tests to prevent deaths linked to gene–drug incompatibility. A decision-analytic approach was constructed to estimate both the number of prevented gene–drug-related deaths and the associated financial cost over 1 year in the Dutch healthcare setting. The tested strategy involved a single-gene assay—CYP2C19, DPYD, TPMT, or UGT1A1—used to tailor therapy according to DPWG recommendations for Dutch patients beginning treatment with clopidogrel, capecitabine, systemic fluorouracil, azathioprine, mercaptopurine, tioguanine, or irinotecan. Among 148,128 individuals starting one of the seven drugs in a single year, national spending on PGx testing, interpretation, and medications would rise by €21.4 million. Within this cohort, 35,762 (24.1%) would receive an altered drug or dosage. PGx-informed prescribing would reduce mortality attributable to gene–drug mismatch by 10.6% (DGI-specific span: 8.1–14.5%), ultimately avoiding 419 deaths annually (0.3% of all initiators). The estimated economic value equates to €51,000 for each gene–drug-related death prevented (DGI-specific range: €-752,000 to €633,000). National use of PGx-based prescribing for DGIs labeled “essential” could prevent death in roughly 0.3% of new users of these medications, at a cost level considered acceptable for interventions of this scale.

**Keywords:** Pharmacogenomics, Cost-effectiveness, Drug-related mortality, Adverse reactions, Precision therapy

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### Introduction

PGx-oriented treatment strategies use inherited genomic information to refine medication choice and dosage [1, 2]. This approach reduces reliance on empirical drug-selection practices and lowers the chance of inadequate therapeutic response or adverse drug reactions (ADRs) [3]. ADRs remain a major medical and financial concern, frequently contributing to emergency visits and hospital stays [4-6]. In the United States alone, associated costs have been projected between \$30 billion and \$136 billion annually [7]. Numerous prospective investigations demonstrate that specific DGIs influence optimal dosing [8-12] or drug selection [13, 14]. Clinical guidelines from CPIC [15, 16] and the DPWG [17-19] provide frameworks for translating PGx findings into treatment decisions. Target populations proposed for PGx screening include cardiology [20], oncology and supportive care [21, 22], and older or polypharmacy patients [23]. Despite these efforts, uncertainty persists regarding which PGx tests warrant priority for routine adoption [24]. To offer clearer direction, the DPWG created the Clinical Implication Score, highlighting DGIs labeled “essential,” for which single-gene testing should be performed prior to treatment to determine both drug type and dosage [19]. This score reflects clinical risk, evidence strength, the number needed to genotype to prevent a CTCAE  $\geq 3$  ADR, and the extent to which PGx guidance appears in drug

labeling. These “essential” DGIs involve medications with high potential for serious outcomes, including gene–drug-related mortality, making them a minimum recommended set for pre-treatment PGx evaluation.

Although several hurdles to incorporating pharmacogenomic testing have been reduced, performing pre-treatment PGx evaluations for every DGI labeled “essential” has not yet become part of everyday clinical workflow, and significant obstacles still obstruct broader use [25-27]. One of the most persistent issues is that single-gene PGx analyses are often not reimbursed, even though extensive economic research has already been published on them [28, 29]. Demonstrating the overall health impact and financial justification for implementing PGx for “essential” DGIs on a large scale could help motivate coverage decisions. Among all possible outcomes, the influence on mortality is likely the most persuasive metric.

Prior work has outlined how often DGIs would arise across a population [30-32], and cost-effectiveness calculations for individual single-gene situations are available [28, 29]. However, what remains unknown is the cumulative clinical and economic effect of adopting all “essential” DGIs together in routine practice. For this reason, our study focuses on estimating the combined influence and cost-effectiveness of PGx testing for DGIs classified as “essential” in preventing deaths linked to gene–drug incompatibility, assuming nationwide implementation in the Netherlands. A decision-analytic model was created that integrates three components: literature-derived mortality probabilities, Dutch prescription records to determine drug-initiation rates, and phenotype frequencies obtained from a Dutch cohort.

## Materials and Methods

### Study design

To determine how many deaths might be avoided—and at what financial cost—we constructed a decision-analytic framework comparing standard practice with PGx-guided selection of initial dosing and agents for “essential” DGIs over a 1-year period among Dutch patients beginning relevant therapies. DGIs were included only if:

1. The Clinical Implication Score identified them as “essential,” meaning pre-therapy genotyping is recommended by the DPWG; and
2. The DGI carried clinical relevance level F (CTCAE Grade 5), indicating that at least one predicted phenotype has a documented risk of fatality when exposed to the interacting drug.

Applying these criteria generated a set of four genes (CYP2C19, DPYD, TPMT, UGT1A1) and seven medications (clopidogrel, capecitabine, systemic fluorouracil, azathioprine, mercaptopurine, tioguanine, irinotecan). **Table 1** summarizes all selected pairings. When DPWG guidance listed both dose reduction and switching therapies as options, the model adopted dose reduction as the default intervention.

**Table 1.** Overview of selected “essential” gene–drug combinations, the associated potential clinical outcomes, and phenotype-specific recommendations.

Drug	Gene	Predicted Phenotype	Actionable DGI	DPWG Guidance	Most Serious Preventable Outcome Potentially Resulting in Gene–Drug-Related Mortality
Azathioprine	TPMT	TPMT EM	No	–	–
		TPMT IM	Yes	Reduce dose to 50%	Severe marrow suppression
		TPMT PM	Yes	Lower dose to 10% or use alternative therapy	Severe marrow suppression
Capecitabine	DPYD	DPYD GAS 0	Yes	Switch to another drug	Fluoropyrimidine-associated toxicity
		GAS 0.5 / PHENO	Yes	Titrate dose according to DPD status	Fluoropyrimidine-associated toxicity
		DPYD GAS 1.0	Yes	Reduce dose by 50%	Fluoropyrimidine-associated toxicity
		DPYD GAS 1.5	Yes	Reduce dose by 50%	Fluoropyrimidine-associated toxicity
		DPYD GAS 2.0	No	–	–

<b>Clopidogrel</b>	CYP2C19	CYP2C19 EM	No	–	–
		CYP2C19 IM	Yes	Increase dose to 200% or choose an alternative agent	–
		CYP2C19 PM	Yes	Use alternative therapy (ticagrelor, prasugrel, or dipyridamole)	Cardiovascular mortality
		CYP2C19 UM	No	–	Cardiovascular mortality
<b>Fluorouracil</b>	DPYD	DPYD GAS 0	Yes	Substitute with another drug	Fluoropyrimidine-associated toxicity
		GAS 0.5 / PHENO	Yes	Adjust dose based on DPD function	Fluoropyrimidine-associated toxicity
		DPYD GAS 1.0	Yes	50% dose reduction	Fluoropyrimidine-associated toxicity
		DPYD GAS 1.5	Yes	50% dose reduction	Fluoropyrimidine-associated toxicity
		DPYD GAS 2.0	No	–	–
<b>Irinotecan</b>	UGT1A1	UGT1A1 *1/*1, *1/*28, *28/*28	No / Yes / Yes	– / – / Reduce to 70%	– / – / Severe bone-marrow suppression plus diarrhea
		UGT1A1 IM	No	–	–
		UGT1A1 PM	No	Reduce dose to 6%	Severe marrow toxicity and diarrhea
<b>Mercaptopurine</b>	TPMT	TPMT EM	No	–	–
		TPMT IM	Yes	Cut dose to 50%	Severe myelosuppression
		TPMT PM	Yes	Reduce dose to 10% or use an alternative	Severe myelosuppression
<b>Tioguanine</b>	TPMT	TPMT EM	No	–	–
		TPMT IM	Yes	Halve the dose (50%)	Severe myelosuppression
		TPMT PM	Yes	Reduce dose to 10% or select an alternative agent	Severe pancytopenia

aClinical relevance score: CTCAE, 5 (death). Abbreviations: DGI, drug–gene interaction; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; UM, ultra-rapid metabolizer; DPWG, Dutch Pharmacogenetics Working Group; GAS, gene activity score.

#### Decision analytic model

The procedure outlined below was used to estimate how many deaths resulting from gene–drug incompatibility could be avoided annually:

$$N_{\text{GDRDP}} = \sum_{\text{Drug}=1}^7 N_{\text{Drug}} \times \sum_{\text{Pheno}} P_{\text{Pheno}} \times (AR_{\text{Drug,Pheno}}^{\text{SoC}} - AR_{\text{Drug,Pheno}}^{\text{PGx}}) \quad (1)$$

$N_{\text{GDRDP}}$  = gene-drug-related deaths prevented;

$N_{\text{Drug}}$  = total count of individuals beginning therapy;

$P_{\text{Pheno}}$  = distribution of predicted phenotype categories;

AR = absolute probability of a gene–drug-related fatal event within a 1-year period;

SoC = standard treatment pathway;

PGx = prescribing based on pharmacogenomic test–guided selection of starting dose and medication;

Drug, Pheno = values corresponding to a particular drug and its associated predicted phenotype group.

The expression below was applied to estimate the financial cost associated with preventing gene–drug-related mortality over a 1-year horizon:

$$\text{Cost} = \sum_{\text{Drug}=1}^7 N_{\text{Drug}} \times \sum_{\text{Pheno}} P_{\text{Pheno}} \times \text{Cost}_{\text{PGx}} + \text{Cost}_{\text{HCP}} + \text{Cost}_{\text{Drug,Pheno}}^{\text{PGx}} - \text{Cost}_{\text{Drug,Pheno}}^{\text{SoC}} \quad (2)$$

NDrug refers to the count of individuals starting a medication; PPheno indicates the assigned predicted phenotype group; CostPGx represents the expense of a single-gene pharmacogenetic test; CostHCP covers clinician and pharmacist time spent interpreting and discussing clinically relevant PGx findings; PGx denotes pharmacogenomic-guided initial therapy and dose decisions; SoC stands for standard care; Drug, Pheno specifies a given medication combined with a particular predicted phenotype classification. The cost per avoided gene–drug–related fatality was determined by dividing overall costs by the number of deaths prevented, calculated both for each DGI separately and in aggregate.

### *Model inputs*

#### *Number of patients starting one of the seven medications in the netherlands*

Annual counts of new starters for each of the seven medicines were derived by multiplying the annual user totals by the proportion of initiators among users. Yearly user data were obtained from the Dutch national GIP database using the most recent reports available: azathioprine, clopidogrel, systemic fluorouracil, and irinotecan from 2018; mercaptopurine and tioguanine from 2017; and capecitabine from 2014 [33]. Because fluorouracil usage in the GIP dataset combines systemic and dermatologic forms, we adjusted the total by applying the percentage of systemic users recorded at Leiden University Medical Center (LUMC) in 2018 to remove cutaneous use.

Initiator-to-user ratios were extracted per drug from the LUMC electronic medical records (EMR) covering 2013–2018. “Users” were defined as anyone with at least one prescription for the medication in the EMR during this period, and “initiators” were those without any prescription prior to 2018.

#### *Predicted phenotype category frequencies*

Predicted phenotype distributions for the included genes originated from a Dutch cohort ( $n = 1,023$ ) [34]. The variant set used for phenotype determination has been documented previously. Genotypes were converted to predicted phenotype categories using functional interpretations consistent with DPWG guidance [17, 19].

#### *Risk of gene–drug–associated mortality*

**Table 1** outlines the most serious clinical outcome linked to each “essential” DGI in patients treated under standard care, as reported in the evidence supporting DPWG recommendations. These guidelines advise either dose modification or choosing an alternate therapy to lower the likelihood of both fatal gene–drug reactions and other clinically significant ADRs. For the model, we collected the absolute one-year risk of gene–drug–related death for both PGx-guided therapy and SoC (PGx-uninformed), stratified by predicted phenotype group, given that mortality risk differs among phenotypes. For instance, toxicity from fluoropyrimidines rises as DPYD gene activity scores (GAS) decrease. When PGx-based dosing is implemented, individuals with an actionable phenotype (DPYD GAS 0–1.5) experience reduced toxicity risk compared with actionable individuals receiving standard dosing. Those with a non-actionable phenotype (DPYD GAS 2) retain the same mortality risk regardless of testing, because dosing remains unchanged.

Thus, absolute mortality risks were extracted per phenotype category across three groups:

1. tested-actionables (e.g., DPYD GAS 0, 0.5, 1, 1.5 receiving PGx-guided reduced dosing),
2. non-actionables (e.g., DPYD GAS 2 with standard dosing), and
3. untested-actionables (e.g., DPYD GAS 0, 0.5, 1, 1.5 with unadjusted dosing).

Actionable gene–drug combinations are summarized in **Table 1**.

A structured procedure was applied to identify publications underlying the DPWG guidance that were appropriate for extracting risk estimates. In summary, the process consists of six sequential steps to identify studies from which absolute mortality risks for each tested and untested predicted phenotype group can be obtained. The methodological robustness of the included studies decreases with each step and aligns with the DPWG evidence grading system [17, 18]. The first two steps focus on studies with mortality as the primary endpoint, the next two select studies examining intermediate outcomes associated with fatal events, and the final steps rely on extended literature searches or inferred estimations. Risk extraction follows the approach appropriate to each step. Each derived absolute gene–drug–related mortality risk is assigned a certainty rating corresponding to the step in which the source was selected, with scores ranging from 4 (high confidence) to 0 (very low confidence). A combined

certainty score per DGI is calculated by averaging the certainty values across all tested and untested predicted phenotype categories.

#### *Predicted phenotype category frequencies*

Frequencies of predicted phenotypes for the included genes were obtained from a Dutch cohort (n = 1,023). The specific variants used for phenotype determination are described elsewhere [35]. Genotype-to-phenotype translation followed functional classifications from the DPWG recommendations.

#### *Costs*

Cost estimates were generated from a healthcare-system viewpoint using a 1-year time horizon and are presented in Euros. Prices for single-gene PGx tests were sourced from LUMC test fees from 2018 and Dutch Healthcare Authority (NZa) listings; these covered sampling, analysis, phenotype reporting, and dose guidance sent to the requesting pharmacist.

Pharmacist time for documenting and discussing findings with both the clinician and patient was fixed at 18 minutes, while physician time for reviewing results with the pharmacist was set at 6 minutes. These time inputs were multiplied by standardized hourly wages for Clinical Pharmacists and Medical Specialists in Dutch Academic Hospitals (2019) [36]. Medication costs for both standard care and PGx-based treatment were calculated for 1 year, using dosing typical for the main indication, assuming a 75 kg individual with a 1.7 m<sup>2</sup> body surface area. Drug prices were taken from the national registry [37] using the lowest-cost appropriate formulation.

#### *Model assumptions*

The model assumed 100% uptake of PGx testing among new drug starters, 100% adherence to DPWG recommendations, and protocol-aligned dosing for indications represented in the studies from which risk estimates were obtained. The target population was assumed to be Caucasian, with comedication patterns resembling those in the original study cohorts used for risk extraction.

#### *Funding and ethical approval*

The project received support from the European Community's Horizon 2020 Program under grant No. 668353 (U-PGx). The funding body did not influence study design, execution, or reporting. Ethical approval was unnecessary, as all input data were sourced from the public domain.

## Results and Discussion

Based on **Table 2**, within a national population of 17 million people, 148,128 individuals begin treatment with one of the seven evaluated medications annually, with clopidogrel users making up the majority (79.6%).

**Table 2.** Overall expenditures for PGx testing, clinician interpretation, and drug therapy.

Drug	Number of Initiators	PGx Test Cost (€ per Initiator)	Cost for HCP Interpretation of Actionable Result (€)	Typical Drug Expense in SoC (€ per Initiator, 1 year)	Drug Expense with PGx-Guided Therapy (€ per Initiator, 1 year)	Change in Average Drug Costs (SoC – PGx) (€; % saved)	Total Costs for All Initiators (€)
<b>Azathioprine</b>	6,979	132	1	248	237	11 (4.6%)	854,659
<b>Capecitabine</b>	8,860	132	1	1,204	1,158	46 (3.9%)	775,246
<b>Clopidogrel</b>	117,900	132	5	15	38	–24 (–62%)	18,923,430
<b>Fluorouracil (systemic)</b>	6,765	132	1	82	79	3 (4.0%)	880,112
<b>Irinotecan</b>	2,593	66	2	14,842	14,588	253 (1.7%)	–481,019
<b>Mercaptopurine</b>	2,177	132	1	1,956	1,875	81 (4.3%)	114,172
<b>Tioguanine</b>	2,854	132	1	1,088	1,080	7 (0.7%)	359,471
<b>TOTAL (all initiators)</b>	148,128	19,381,790	586,167	60,519,056	61,977,169	–1,458,113	21,426,070

<b>Average per Initiator (€)</b>	–	131	16a	409	418	10	145
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PGx, pharmacogenomic.

<sup>a</sup>Note: only those with an actionable drug-gene interaction will be interpreted by an HCP.

<sup>b</sup> $[\text{cost drugs standard of care}] - [\text{cost drugs PGx-guided}] * [\text{N drug initiators}]$ .

<sup>c</sup> $[\text{cost PGx test}] + [\text{cost pharmacist and physician time}] - [\text{cost drugs}]$ .

### Impact on costs

The combined annual expense of single-gene PGx assays, interpretation time, and drug costs totals €21.4 million (mean €145 per initiator). Of this, single-gene testing accounts for 90.7% (€19.4 million, mean €131 per person). Among all drug starters, 35,762 individuals (24.1%) would have an actionable DGI needing dose modification or an alternative medication. The professional time required to review and communicate these actionable results is €586,000 (about €16 per actionable case). The net increase in medication expenses due to PGx-guided treatment equals €1.5 million (roughly €10 per patient), consisting of €2.4 million in extra spending on alternative therapies and €941,000 saved by dose reductions. Most DGIs demonstrate cost-savings with PGx-guided therapy (0.7–4.6% savings range), except the clopidogrel–CYP2C19 pair, where drug spending rises by €2.8 million (€24 per initiator, +162%) compared with standard care. For the irinotecan–UGT1A1 combination, drug savings in the PGx arm exceed testing and HCP interpretation costs, generating a net saving of €481,000.

### Cost-effectiveness analysis

Avoiding 419 deaths at an added expenditure of €21.4 million yields a cost-effectiveness ratio of €51,000 per prevented fatal event (range by DGI: €–752,000 to €633,000).

For irinotecan–UGT1A1, PGx guidance decreases both mortality and spending, producing a negative (i.e., cost-saving) ratio.

Implementing PGx-based first-line dose and drug choices for “essential” DGIs across the country could prevent 419 deaths annually (0.3% of initiators) at a cost of €51,000 per death averted. The weighted certainty score is 2.5 (moderate confidence).

In high-income health systems, an intervention is typically considered economically reasonable if the cost per gained QALY is between €20,000–60,000 [38]. Because PGx-guided prescribing avoids fatal ADRs, it is expected to produce substantial QALY gains, which depend on survival time added following prevention of toxicity. The seven medications assessed are treatments for severe illnesses; thus, effective and safe therapy typically confers meaningful—though below-average—life expectancy. Given this context, the €51,000 cost per death prevented falls well within accepted thresholds and represents a cost-effective strategy.

### Comparison to current literature

To date, this is the first assessment quantifying both the total clinical benefit and overall cost-effectiveness of national PGx-guided initiation for DPWG-defined “essential” DGIs with respect to mortality.

Previous large-scale evaluations have estimated how often actionable DGIs would occur at a national level [30–32]. Bank *et al.* projected that adopting all DPWG recommendations in the Netherlands would yield actionable DGIs in 23.6% of new prescriptions for PGx-relevant medicines [32], though clinical outcomes were not analyzed. Earlier economic analyses focused on single DGIs rather than collective impact. These include studies of:

- HLA-B\*57:01 before abacavir [39],
- HLA-B\*58:01 before allopurinol [40],
- HLA-B15:02 / HLA-A31:01 before carbamazepine,
- CYP2C9 / VKORC1 for warfarin dosing [41].

However, none of these were categorized as “essential” by the DPWG and thus were not part of this study. Consistent with the DGIs examined here, previous research has demonstrated cost-effectiveness for:

- UGT1A1 testing for irinotecan [42, 43],
- CYP2C19-guided clopidogrel management [44, 45],
- TPMT-based thiopurine dosing [46].

While DPYD-guided dosing has been evaluated for cost minimization [47, 48], its formal cost-effectiveness remains unknown.

### *Model design and inputs*

The decision model focuses specifically on gene–drug–related mortality. Other outcomes that could improve with PGx-guided prescribing—such as reductions in nonfatal adverse drug reactions (ADRs) or insufficient therapeutic response—were not included. Because these non-lethal but likely more frequent gene–drug toxicities were excluded, the projected clinical benefits of PGx may be underestimated. Including such events would further strengthen the argument that PGx-guided therapy is cost-effective for “essential” DGIs.

At the same time, while PGx-based adjustments can reduce gene–drug–linked ADRs, they may theoretically heighten risks such as reduced therapeutic effect or the emergence of different ADRs. These factors were not incorporated, which could lead to some degree of overestimation. Regarding reduced efficacy, similar drug exposure and benefit–risk balance are expected in IMs and PMs receiving reduced doses and in EMs on standard doses, as demonstrated prospectively [12]. Drugs with steep dose–response characteristics or where standard dosing does not reach maximal receptor occupancy may be most susceptible to diminished efficacy [49]. Overall, excluding this endpoint likely has minimal influence on the model because efficacy formed part of the composite intermediate outcome (death, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) for the primary DGI (clopidogrel–CYP2C19).

Possible underestimation from not considering other ADRs can be exemplified by ADRs linked to PGx-based substitutions. For instance, CYP2C19-tailored use of clopidogrel versus ticagrelor or prasugrel was non-inferior at 12 months for thrombotic outcomes, but ticagrelor or prasugrel produced more minor bleeding episodes [50]. In this scenario, omitting minor bleeding does not bias the model because such events do not contribute to drug-related mortality.

The model uses a 1-year time horizon, aligning with follow-up in the supporting clinical trials. Ignoring events beyond one year may underestimate benefits. Conversely, using a one-year frame likely overstates cost savings, because our findings show an overall cost increase driven particularly by the €2.8 million annual rise in drug spending for PGx-guided alternatives to clopidogrel. Since clopidogrel therapy typically continues lifelong after a Transient Ischemic Attack, these added medication costs would accumulate with longer time horizons. Furthermore, we did not consider dose or drug changes that might occur in standard care without PGx testing. If clinicians had made such adjustments within the same 1-year period, the relative advantage of the PGx strategy would diminish. This may apply to drugs like fluoropyrimidines and thiopurines, which may be titrated based on clinical or laboratory markers (e.g., hematologic counts) under standard practice.

Several assumptions may influence generalizability. First, for absolute risk extraction, each drug initiator was assumed to have a single specific indication with a corresponding standard dose. Yet some evaluated drugs have multiple clinical uses, and patients with other indications may differ in baseline mortality risk due to comorbidities or closer monitoring. PGx benefit may also vary with indication-specific dosing. For example, thiopurine risk estimates were derived from studies in Inflammatory Bowel Disease, but some users receive thiopurines for Acute Lymphatic Leukemia or Rheumatoid Arthritis, where dosing is higher, and monitoring is more intensive, likely altering death risk.

Second, the target population was assumed to be Caucasian, and absolute-risk publications were selected accordingly. Because allele frequencies differ across populations, extrapolation to ethnic groups not represented in the source datasets is inappropriate. While TPMT allele distributions are relatively stable worldwide [51], actionable phenotype frequencies are higher for UGT1A1 in Blacks and Hispanics [52], CYP2C19 in Asians [53], and DPYD in Africans [54]. Consequently, the current model underestimates cost-effectiveness in these populations.

Third, the structure of the model reflects the Dutch healthcare system. Since PGx implementation outcomes may depend heavily on system quality, results should be extrapolated only to countries with comparable healthcare performance. If both health-system characteristics and population ethnicity mirror those of the Netherlands, scaling results proportionally to a population of 17 million is reasonable.

In this analysis, we estimated 148,128 patients per year initiating one of the seven drugs, with 24.1% showing an actionable DGI. A prior report estimated 3,628,597 new prescriptions annually in the Netherlands for 45 drugs with DPWG recommendations, with a similar proportion of actionable DGIs (23.6% vs. 24.1%) [32]. This discrepancy arises because that study relied on community pharmacy data from primary care only, whereas our dataset covers both primary and hospital care. In addition, the previous work excluded drugs predominantly administered in hospital settings, including capecitabine, fluorouracil, and irinotecan.

Despite initial differences, comparable yearly initiator counts have been documented across settings: azathioprine (6,943 vs. 6,979), clopidogrel (98,709 vs. 117,900), mercaptopurine (2,598 vs. 2,177), and thiopurines (1,883 vs. 2,854). These figures confirm that the initiator estimates used in our model are robust.

In this analysis, we restricted cost inputs to PGx testing, healthcare professional interpretation, and medication expenses, thereby omitting hospitalization costs related to gene–drug-associated ADRs that do not result in death. Even with this narrow viewpoint, we consider our cost estimates conservative. For instance, PGx test pricing was derived from 2018 LUMC rates, which were higher than those available in 2020, aligning with expectations that genetic testing has become cheaper over time. Although based on a different PGx strategy and patient population, earlier work estimated PGx-related savings at \$218 per tested individual [23]. Additional savings not included in our model are reductions in healthcare use from fewer dose adjustments or less clinical monitoring [48]. Consequently, our calculations likely underestimate both the cost needed to prevent gene–drug-related mortality and the broader cost-saving potential.

### *Limitations*

A major limitation of this approach is that many publications used for extracting risk of gene–drug-related death focused on intermediate outcomes rather than direct drug-induced mortality (corresponding to certainty scores of 3 or below). PGx trials powered to detect mortality would require very large cohorts, making them unlikely. Thus, we relied on extracting absolute risks of intermediate outcomes—such as treatment-induced myelosuppression—known to precede gene–drug-related fatality and then multiplied these by the estimated risk of death following such events. While the extraction of intermediate and mortality risks followed a structured method based on DPWG literature, the estimation of mortality following intermediate outcomes depended on the investigator’s judgment and was not systematic. Another constraint is that most effect-size estimates for PGx-guided prescribing derive from observational data. Ideally, they would be taken from randomized controlled trials directly comparing PGx guidance with usual care. However, such RCTs for every individual DGI are improbable, supporting the use of observational evidence.

### *Future research*

This work focused on seven “essential” DGIs in single-gene contexts, though numerous other actionable DGIs exist that aim to mitigate non-fatal ADRs. Since 2005, the DPWG has generated 63 recommendations [17-19], and the CPIC has published 73 recommendations [15, 16]. PGx implementation is expected to shift from reactive single-gene testing toward pre-emptive multi-gene panel approaches, where several pharmacogenes are assessed simultaneously, and results are integrated into the EMR in anticipation of future prescribing. Such pre-emptive panels may improve workflow and enhance cost-efficiency, supported by evidence that patients accumulate numerous prescriptions with potential DGIs throughout life [30, 31] and that the incremental cost of adding more pharmacogenes is minimal [24]. However, cost-effectiveness may be reduced because a portion of individuals will not ultimately benefit from testing. As PGx implementation evolves toward panel-based strategies, future analyses should estimate the economic value of multi-gene panels for remaining DGIs with established guidance, ideally across longer time spans.

### **Conclusion**

Using a decision-analytic model, we evaluated the cost-effectiveness of nationwide PGx-guided initial therapy for seven DGIs identified as “essential” by the DPWG in the Netherlands. Our findings indicate that broad adoption of PGx-informed dosing and drug choice for these “essential” DGIs could prevent 419 deaths (0.3% of drug starters) at an acceptable cost of €51,000 per death prevented. The average certainty score was 2.5 (moderately certain). These results support nationwide implementation of PGx-guided initial prescribing for “essential” DGIs.

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