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Cost-Effectiveness of an Expanded Pharmacogenomic Panel (HLA-B, HLA-DQB1, and SLCO1B3-SLCO1B7) for Preventing Clozapine-Induced Agranulocytosis/Granulocytopenia: A 10-Year Decision-Analytic Model

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ABSTRACT

Growing efforts have focused on uncovering pharmacogenetic contributors that heighten the likelihood of clozapine-associated agranulocytosis or granulocytopenia (CIAG). Three markers—the SLCO1B3-SCLO1B7 polymorphism (rs149104283) and specific single–residue substitutions in the human leukocyte antigen (HLA) region, HLA-DQB1 (126Q) and HLA-B (158T)—have been linked to elevated CIAG risk. In this analysis, we examined both the clinical impact and economic implications of supplementing existing HLA-based screening with the SLCO1B3-SCLO1B7 variant as an expanded pharmacogenomic (PGx) approach, and assessed outcomes in a population of individuals with schizophrenia using clozapine as a third-line therapy. The decision framework incorporated deterministic and probabilistic sensitivity assessments to estimate total costs and quality-adjusted life-years (QALYs). Over a 10-year period, the current monitoring program was evaluated against a PGx-based pathway in which all patients receive genetic testing before beginning clozapine. Incorporating the SLCO1B3-SCLO1B7 variant increased CIAG detection sensitivity from 36.0% to 43.0%, reduced specificity from 89.0% to 86.9%, and raised the probability of being cost-effective from 74.1% to 87.8%. The incremental cost-effectiveness ratio was £16,215 per QALY, staying underneath the conventional threshold (£30,000 or US$50,000 per QALY). These findings indicate that adding the SLCO1B3-SCLO1B7 marker to HLA alleles improves pre-emptive test performance and enhances both the clinical and economic utility of PGx-guided clozapine treatment.

Keywords: Clozapine, Agranulocytosis, Granulocytopenia, Genotype testing, PGx, Pharmacoeconomics

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Introduction

Across Western and Asian healthcare systems, roughly 1%–3% of clozapine (CLZ) users develop severe neutropenia during the first few weeks of therapy [1]. Granulocytopenia and agranulocytosis arising from medication exposure represent distinct clinical patterns, with differing causes, risk determinants, progression timelines, and prognostic outcomes. CLZ-related neutropenia generally emerges 1–2 weeks after starting treatment, is more common among individuals of African descent with low baseline leukocyte counts, and is influenced by dose and duration. CLZ-induced agranulocytosis (CIA) tends to appear 2–8 weeks after therapy begins, reflects substantial idiosyncratic and genetic influence, and occurs more frequently in Asians, in women, and in older adults [2]; low initial leukocyte counts do not predict CIA.

A genome-wide association study reported that amino-acid substitutions at HLA-DQB1 (126Q) and HLA-B (158T) [3], along with the SLCO1B3-SCLO1B7 (rs149104283) variant [4], were linked to CIA susceptibility in individuals of European ancestry. The convergence of HLA and SLCO markers with agranulocytosis risk supports an immune-based mechanism combined with modified transporter activity that may alter myeloid precursor behavior, contributing to the unified CIAG phenotype (CIA + clozapine-related granulocytopenia (CIG)). Similar transporter influx variations have been associated with adverse reactions such as simvastatin-related myopathy

[5] and docetaxel-triggered neutropenia [6]. The SLCO1B3-SCLO1B7 variant, an intronic SNP within hepatic transporter genes [4], may help explain neutropenia through altered pharmacokinetics.

Integrating pharmacogenomic (PGx) findings into clinical protocols may decrease unnecessary discontinuation of CLZ due to hematologic concerns and support improved psychiatric outcomes. This is particularly relevant because monitoring guidelines for leukocyte counts differ widely between countries and are often not cost-efficient [7]. In the US, UK, Switzerland, and Japan, HLA-informed monitoring strategies have been shown to outperform absolute neutrophil count surveillance or switching to less potent antipsychotics from a cost-effectiveness standpoint [8, 9].

The present research explored whether integrating SLCO1B3-SCLO1B7 into HLA-based PGx screening provides additional predictive value for CIAG among individuals prescribed CLZ as a third-line agent.

Materials and Methods

Decision analytic model and PGx-based intervention

We assessed both the health impact and cost-effectiveness of adding the SLCO1B3-SCLO1B7 SNP (rs149104283) to existing HLA markers as part of an expanded PGx strategy in long-term CLZ users **(Figure 1)**.

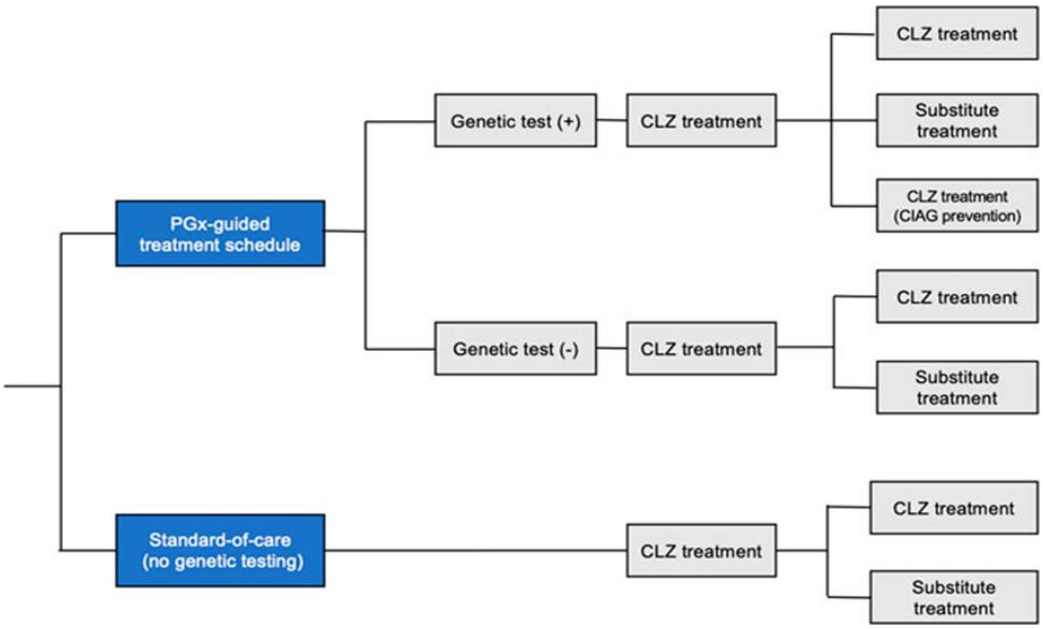


Figure 1. Decision-tree overview comparing the "Standard-of-care (no genetic testing)" pathway with the "PGx-guided treatment schedule." CIAG = clozapine-induced agranulocytosis / granulocytopenia.

To align with UK practice, the model simulated outcomes for adult males and females using CLZ as a third-line therapy under the usual absolute neutrophil count monitoring scheme.

A Markov model was applied to address parameter uncertainty and evaluate how increased PGx sensitivity from adding SLCO1B3-SCLO1B7 affects results. Both deterministic and probabilistic sensitivity analyses generated cost and QALY estimates across 10 years. The existing monitoring process was compared with a PGx-guided protocol in which all patients complete pre-treatment genetic testing before initiating CLZ.

Building on earlier evaluations, the decision framework contrasted two distinct treatment pathways: a "PGx schedule" and the conventional "standard-of-care without genetic testing" [8].

PGx-guided treatment schedule:

Under this option, every patient received a genetic test and was classified according to whether they carried risk alleles. Individuals with these alleles showed a higher likelihood of developing CIAG than non-carriers, although the genetic screening's positive predictive value remained low (roughly 10%), meaning most carriers did not actually progress to CIAG. Because replacing clozapine with another antipsychotic generally results in poorer quality-of-life outcomes, the presence of risk alleles does not automatically lead to stopping CLZ in real-world care. For this reason, the base-case scenario assumed that patients with risk alleles continue CLZ, but that

psychiatrists—being aware of the patient's elevated genetic risk—would exercise heightened vigilance. This increased attention is expected to reduce CIAG incidence. The alleles considered high-risk included rs149104283 and the HLA variants HLA-DQB1 (126Q) and HLA-B (158T). Clinicians are assumed to apply stricter hematologic surveillance or use short "temporary interruptions" of CLZ when necessary, thus avoiding complete withdrawal. A CIAG prevention effect of 30% was applied, consistent with prior evidence [8]. Monitoring followed the CPMS protocol: weekly blood tests during the first 18 weeks, followed by testing every 2 weeks thereafter. When CIAG did occur, CLZ was stopped and replaced by an alternative antipsychotic.

Most patients, however, would not possess any of the risk alleles and would therefore continue under the Standard-of-care (no genetic testing) described below.

Standard-of-care (no genetic testing):

This reflects the protocol widely used in Japan and many Western healthcare systems. During the first 18 weeks of CLZ therapy, blood counts are checked weekly and then biweekly after that period. If either the white blood cell count (WBC) falls below 3,000/mm³ or the absolute neutrophil count (ANC) drops under 1,500/mm³, CLZ is discontinued immediately. Rechallenge for CIAG cases remains prohibited unless formally approved by the CPMS based on clinical history. A recent revision to UK criteria for access to the clozapine non-rechallenge database has been modeled elsewhere [10]. In these analyses, discontinuation based solely on the WBC threshold (<3,000/mm³) was omitted because WBC alone rarely triggers termination; in such circumstances, ANC almost always reaches the critical 1,500/mm³ cutoff [11]. All patients begin on CLZ, and those who develop CIAG switch to a substitute antipsychotic.

Population, model structure, and parameters

The study population matched that used in earlier work [9]: adult men and women in the UK diagnosed with treatment-resistant schizophrenia and eligible for CLZ. A Markov model, operating in 1-month cycles, was used to estimate movement between health states depending on whether patients remained on CLZ or transitioned to a substitute medication.

Key determinants previously recognized include:

1. CIAG prevalence: 3.43% [12];
2. cost of CIAG management: £469.48 [13];
3. daily cost of CLZ: £1.23 [14, 15];
4. daily cost of substitute antipsychotics: £5.11, based on weighted prescribing in the UK (risperidone 21.5%, aripiprazole 10.8%, olanzapine 19.7%, quetiapine 42.8%, amisulpride 5.2%) [14, 16];
5. genetic testing cost: £110, assuming £100 for HLA testing and £10 for rs149104283;
6. monthly cost of routine blood testing: £10.6;
7. utility for CLZ users: 0.693, derived from EQ-5D [17];
8. utility for substitute therapy: 0.560, estimated from standard gamble, rating scales, and paired comparisons [18];
9. CIAG prevention rate: 30% [8].

Medical expenditures were calculated using direct Medical Care Expenditure guidelines from the UK National Health Service (April 2019) [19].

Table 1. Input parameters.

Parameter	Base-case value	Included in probabilistic sensitivity analysis	Distribution type	Distribution parameters	Source(s)
Prevalence of clozapine-induced agranulocytosis/granulocytopenia (CIAG)	3.43%	No	–	–	[12]
Cost of managing one episode of CIAG (£)	469.48	Yes	Gamma	$\alpha = 4$; $\lambda = 0.0085$	[13]
Daily cost of clozapine (£/day)	1.23	Yes	Gamma	$\alpha = 37.8$; $\lambda = 30.75$	[14, 15]

Daily cost of alternative antipsychotic therapy (£/day)	5.11	Yes	Gamma	α = 104.4; λ = 20.44	[14, 16]
Cost of preemptive pharmacogenomic panel (£)	110	No	–	–	Institutional data
Cost of mandatory hematological monitoring (£/month)	10.6	No	–	–	Institutional data
Utility value for patients stable on clozapine	0.693	Yes	Beta	α = 575; β = 255	[9]
Utility value for patients on alternative antipsychotic treatment	0.560	Yes	Beta	α = 86; β = 67	[9]
Proportion of CIAG cases preventable by current blood monitoring	30%	Yes	Beta	α = 24.9; β = 58.1	[8]
Sensitivity of the expanded panel (HLA + SLCO1B3-SLCO1B7)	43.0%	Yes	Beta	α = 169.13; β = 223.87	[3, 4]
Specificity of the expanded panel (HLA + SLCO1B3-SLCO1B7)	86.9%	Yes	Beta	α = 15531.77; β = 2342.23	[3, 4]

aBased on combined risk contributions of HLA-DQB1 (126Q), HLA-B (158T), and rs149104283. CIAG = clozapine-induced agranulocytosis/granulocytopenia; CLZ = clozapine.

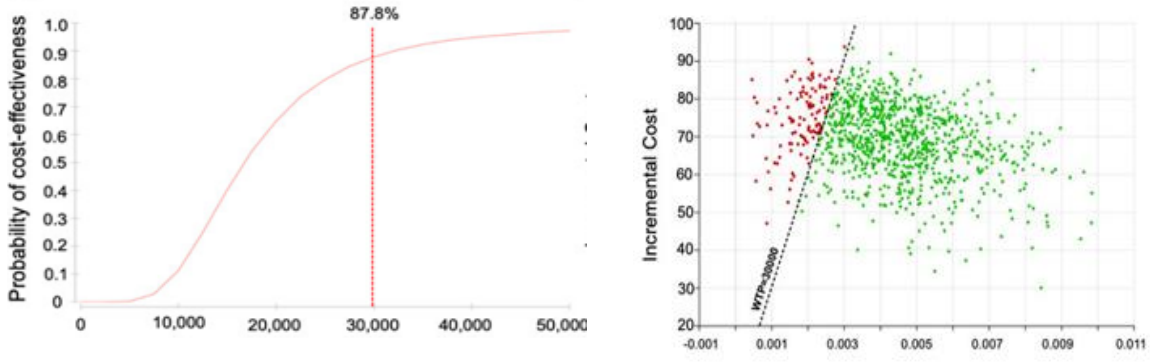
Aggregated sensitivity and specificity for the allelic markers [rs149104283 [4], HLA-DQB1 (126Q), and HLA-B (158T) [3]] were derived using the following calculations:
Sensitivity = $1 - (1 - \text{Sensitivity}_1) \times (1 - \text{Sensitivity}_2) = 1 - (1 - 0.360) \times (1 - 0.109) = 0.430$
Sensitivity_1 = sensitivity attributed to HLA-DQB1 (126Q) and HLA-B (158T) = 0.36
Sensitivity_2 = sensitivity attributed to rs149104283 = 0.109
Specificity = $\text{Specificity}_1 \times \text{Specificity}_2 = 0.890 \times 0.976 = 0.869$
Specificity_1 = specificity of HLA-DQB1 (126Q) and HLA-B (158T) = 0.890
Specificity_2 = specificity of rs149104283 = 0.976
The model produced average cost-per-patient and QALY-per-patient values, which were then applied to compute the incremental cost-effectiveness ratio (ICER) over a 10-year horizon.
A probabilistic sensitivity assessment was executed with Monte Carlo sampling, using either 95% confidence bounds or plausible clinical ranges for each parameter. A total of 100,000 simulations were run based on randomly generated inputs. After estimating costs and QALYs for both comparators, ICER values were calculated using:
Cost(PGx-guidedtreatmentschedule)−Cost(Standard-of-care)QALY(PGx-guidedtreatmentschedule)−QALY(Standard-of-care)
A 3.5% discount rate was applied to all costs and QALY outcomes. The willingness-to-pay threshold was set at £30,000 per QALY, in alignment with UK guidance [19].
The combined CLOZUK and CIAG Consortium (CIAC) dataset (229 cases, 13,553 controls) provided 80% power to identify variants showing a relative risk (RR) > 3 with a minor allele frequency (MAF) above 0.10 at $p < 5 \times 10^{-8}$. Variants with RR ≤ 3 and MAF ≤ 0.10 were categorized as "undetected risk variants," presumed to become detectable with larger sample sizes across different RR and allele frequency combinations. To estimate the minimum case counts needed, we applied the Genetic Association Study Power Calculator [20].
Sensitivity and specificity computed from the MAF and RR of these "undetected risk variants," combined with values from HLA-DQB1 (126Q), HLA-B (158T), and SLCO1B3-SLCO1B7, produced adjusted diagnostic performance metrics. Additional genetic testing costs were varied between £110 and £130 to account for uncertainty.
All cost-effectiveness analyses adhered to CHEERS reporting requirements [21]. TreeAgePro® (2019 release, TreeAge Software Inc., MA, USA) was employed for constructing the model, conducting sensitivity evaluations, and running simulations.

Results and Discussion

Our results indicated that adding the SLCO1B3-SCLO1B7 marker to the HLA variants raised CIAG sensitivity from 36.0% to 43.0%, while specificity declined from 89.0% to 86.9%. Using a CIAG incidence of 3.43% and a sensitivity of 0.43, the required number of individuals needing genotyping was calculated as (100 / (3.43 × 0.43)). This corresponded to 68 patients needing screening to prevent one CIAG case and 232 to avert one episode of

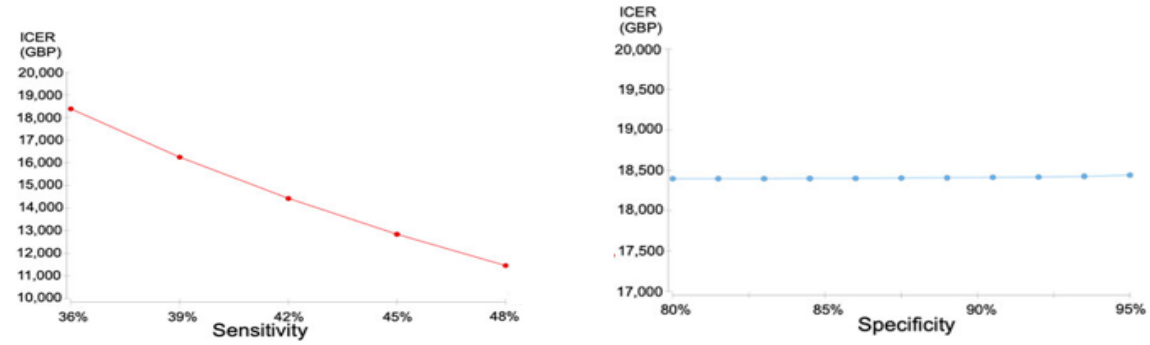
severe CIA (<500/mm³). These approximations align with prior estimates based on agranulocytosis incidence, although earlier single-HLA tests had lower sensitivity [9].

Economically, the probability that the strategy was cost-effective rose from 74.1% to 87.8%, and the ICER was £16,215 per QALY—remaining well below the commonly used £30,000 (or US$50,000) threshold. Consequently, the PGx-guided approach appeared to be a feasible substitute for the existing standard monitoring routine **(Figure 2)**. To assess the influence of reduced specificity, one-way sensitivity analyses were run for sensitivity and specificity separately **(Figure 3)**. Enhancing sensitivity improved ICERs, whereas specificity changes had minimal impact.



a) b)

Figure 2. Outputs from the probabilistic sensitivity evaluation for [HLA-DQB1 (126Q), HLA-B (158T), rs149104283]:
(a) Cost-effectiveness acceptability curve.
(b) Incremental cost-effectiveness scatter plot showing ICERs under and above the WTP threshold (green vs red markers).



a) b)

Figure 3. One-way sensitivity analyses:
(a) Variation of "sensitivities."
(b) Variation of "specificities." ICER = incremental cost-effectiveness ratio.

A hypothetical scenario was also assessed where "undetected risk variants" had RR = 3 and allele frequency = 5%. Incorporating such variants with the HLA set and SLCO1B3-SCLO1B7 increased CIAG sensitivity from 43.0% to 56.8% and lowered specificity from 86.9% to 78.9%. Under these assumptions, expected total costs for the PGx-guided option were £4,278, and QALYs were 5.83134. The estimated ICER was £11,819, and the probability of being cost-effective rose to 94.8%, indicating that even with additional hypothetical risk alleles, the PGx-guided model stayed within accepted cost-effectiveness limits.

Further outcomes related to scenarios with elevated relative risk and higher MAF values are summarized in **Table 2**. The number of cases needed rises substantially when either the relative risk or the allele frequency becomes smaller. Nevertheless, it should be emphasized that whenever the MAF exceeds 2.5%, the ICER values for any relative risk scenario remain lower than the ICER observed in the base model (HLA + SLCO1B3-SLCO1B7 variants).

Table 2. Required sample sizes to attain 80% power across different combinations of relative risk and allele frequency for SNPs, along with the corresponding ICER estimates.

Relative risk	Allele frequency	10%	7.5%	5%	2.5%	1%
3.0	Case	230	270	360	640	1,510
	ICER (£/QALY)	8657.73	9959.48	11759.02	14300.20	16539.54
2.5	Case	330	390	530	950	2290
	ICER (£/QALY)	9368.75	10665.39	12391.99	14831.65	16829.12
2.0	Case	570	690	940	1740	4470
	ICER (£/QALY)	10246.28	11518.55	13155.14	15413.00	17142.65

ICER = incremental cost-effectiveness ratio.

To our knowledge, this analysis represents the first direct comparison of two cost-effectiveness strategies incorporating pharmacogenomic testing for the SLCO1B3-SCLO1B7 variant in addition to single HLA markers. Moreover, in forward-looking scenario evaluations, integrating future risk alleles into the model would further reduce ICER values as an added benefit of expanding PGx information.

The number needed for genotyping differed markedly depending on whether CIAG or CIA alone was considered, due to the distinct prevalence levels (3.43% vs 1%). From an economic perspective, the expanded PGx strategy produced an ICER of £16,215 per QALY, comfortably below the accepted willingness-to-pay benchmark (<£30,000 per QALY or <US$50,000 per QALY). Using a probabilistic approach to jointly vary model inputs allowed us to observe how parameter uncertainty translated into cost and QALY variation. As demonstrated in the cost-effectiveness acceptability curve **(Figure 2)**, adding the SLCO1B3-SCLO1B7 variant increased the likelihood of cost-effectiveness from 74.1% to 87.8%.

Within this modeling framework, the rise in overall test sensitivity—from 36.0% to 43.0%—was the primary factor driving improvement in cost-effectiveness, despite a modest drop in specificity from 89.0% to 86.9%. These findings were reaffirmed through probabilistic sensitivity analysis.

The results further illustrate that incorporating additional "risk" variants enhances PGx test sensitivity as well as economic performance. As highlighted in **Table 2**, even variants with relatively small risks noticeably affect ICER outcomes. However, the achievable sensitivity ceiling is ultimately dictated by emerging PGx discoveries.

Clinicians' prior knowledge of CIAG susceptibility could support broader clozapine use, yielding notable clinical and economic advantages for individuals with treatment-resistant psychosis—such as schizophrenia—or neurodegenerative conditions featuring extrapyramidal symptoms. Although previous work stressed the need for rigorous validation and cost-effectiveness research before widespread PGx adoption [22], our findings advance the evidence base for informed resource distribution and program design [23]. Additionally, the burdensome blood-monitoring protocols associated with clozapine may slow treatment initiation and hinder patient outcomes. Regulatory bodies, including the FDA, have recently revised clozapine monitoring and distribution requirements through updated risk-mitigation frameworks. These include allowing clozapine use in individuals with benign neutropenia and employing algorithmic or AI-assisted tools for those who previously experienced CIAG but benefited from atypical antipsychotics. A recent modeling investigation also showed that clozapine rechallenge success rates—based on thresholds used in the CLZ central non-rechallenge database (CNRD)—were comparable between registrants and non-registrants [10].

Several limitations accompany our evaluation of a preemptively applied PGx-guided clozapine strategy. First, assumptions were necessary because test sensitivity remains incomplete; the inclusion of the SLCO1B3-SCLO1B7 variant means that genotyping accuracy still plays a decisive role in broader implementation. Full withdrawal of blood monitoring is not advisable without preliminary studies and gradual rollouts. Second, long-term registry evidence is limited; therefore, extending the model beyond the 10-year horizon would require unsupported assumptions. Lastly, using a third-party payer perspective prevented us from including intangible costs such as lost productivity or secondary long-term benefits.

Strengths of the study include the use of key inputs derived from a large CIAG consortium and a decision-analytic framework incorporating extensive deterministic and probabilistic sensitivity checks with conservative assumptions. Cost inputs originated from hospital statistics and diagnosis-related group data.

Conclusion

We conclude that integrating additional risk alleles alongside HLA markers enhances test sensitivity and improves both effectiveness and cost-effectiveness for PGx-guided clozapine administration.

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Ethics Statement: None

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