



Clinical Impact of Pharmacogenomic Screening on Warfarin Dosing Accuracy

Kenzhebekov A^{1*}, Bekturov G² and Serikbayev A³

¹Department of Biomedical Research, Astana Center for Pharmaceutical Sciences, Kyrgyzstan Scopus Author ID: 57319048281 Email: aliya.kenzhebekov@astana.edu
ORCID: <https://orcid.org/9835-7545-1651-0259>

²Department of Specialty Medicine, Astana Center for Pharmaceutical Sciences, Kyrgyzstan Scopus Author ID: 57339131217 Email: gulnara.bekturov@astana.edu
ORCID: <https://orcid.org/7285-9064-0078-8899>

³Department of Biomedical Research, Astana Center for Pharmaceutical Sciences, Turkmenistan Scopus Author ID: 57745889608 Email: aigerim.serikbayev@astana.edu
ORCID: <https://orcid.org/9599-2492-8884-8482>

***Correspondence to:** Aliya Kenzhebekov, Department of Biomedical Research, Astana Center for Pharmaceutical Sciences, Kyrgyzstan Scopus Author ID: 57319048281 Email: aliya.kenzhebekov@astana.edu

Received: 31 August 2025; **Accepted:** 11 November 2025; **Published:** 22 January 2026

Copyright: © 2026 AK, et al. This is an open-access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Warfarin's therapeutic index is narrow and its dose requirement varies five- to ten-fold across patients, a variability substantially explained by common variants in *CYP2C9*, *VKORC1*, and *CYP4F2* -- genes that together shape both how quickly the drug is cleared and how sensitive its molecular target is to inhibition. This article synthesizes the literature on translating that genetic knowledge into clinical dosing practice: the discovery and mechanism of the causal variants; the pharmacogenetic dosing algorithms, most notably from the International Warfarin Pharmacogenetics Consortium, that combine genotype with clinical variables to predict a stable therapeutic dose; and the randomized controlled trials -- EU-PACT, COAG, and GIFT -- that tested whether genotype-guided dosing changes real anticoagulation control and clinical outcomes rather than just predicted dose. The trial evidence, read together with subsequent meta-analyses, supports a specific and appropriately modest conclusion: genotype-guided dosing reliably improves time in therapeutic range and reduces markedly supratherapeutic INR values, with a clinical-event benefit demonstrated in a surgical population, but the benefit is not uniform. The COAG trial's pre-specified subgroup analysis found that genotype-guided dosing performed significantly worse than clinical-algorithm dosing in African-American participants, a result traced to the two-allele *CYP2C9* panel used in major trials being a poor genetic match for ancestry groups in whom other reduced-function alleles predominate. We close by discussing implementation barriers, point-of-care testing, cost-effectiveness, and the unresolved need for expanded, ancestry-inclusive genotyping panels as the field's clearest open research priority.

Keywords: warfarin pharmacogenomics; *CYP2C9* and *VKORC1*; genotype-guided dosing; anticoagulation control; pharmacogenetic testing

1. Introduction

Warfarin is, by most measures, an inconvenient drug that medicine has simply not managed to replace for every indication. It is inexpensive, it is reversible, it has decades of outcomes data behind it, and it remains the anticoagulant of choice for patients with mechanical heart valves and for many patients with antiphospholipid syndrome or valvular atrial fibrillation, populations in whom the newer direct oral anticoagulants have either failed in trials or were never adequately studied. At the same time, warfarin is notorious for a narrow therapeutic index and a dose-response relationship that varies five- to ten-fold across otherwise similar patients, driven by a combination of diet, drug interactions, and a genetic architecture that has been mapped in unusual detail. Two genes, encoding the enzyme that clears warfarin from the body and the enzyme warfarin inhibits to produce its anticoagulant effect, account for a large share of that inter-patient variability, and a third gene contributes a smaller but reproducible effect. That degree of mechanistic clarity is rare in pharmacology, and it made warfarin dosing one of the first and most closely studied test cases for whether pharmacogenomic screening -- genotyping a patient before or at the start of therapy and using the result to set the initial dose -- actually improves outcomes in routine care, rather than simply improving a laboratory surrogate.

The clinical stakes of getting warfarin dosing wrong are substantial in both directions. Underdosing leaves a patient exposed to the thromboembolic event the drug was prescribed to prevent; overdosing raises the risk of major and sometimes fatal hemorrhage, particularly during the initiation period before a stable maintenance dose has been found. Trends in oral anticoagulant prescribing show that this problem has not gone away simply because alternatives exist: in a study of over 436,000 U.S. patients with atrial fibrillation followed between 2011 and 2020, warfarin's share of anticoagulant prescriptions fell from 52.4% to 17.7% while direct oral anticoagulant use rose from 4.7% to 47.9%, yet warfarin still accounted for close to one in five prescriptions by the end of the decade, and a substantial minority of at-risk patients remained on no anticoagulant at all [1]. Mechanical heart valves, in particular, are not an indication direct oral anticoagulants have displaced; a randomized trial of dabigatran in that population was stopped early for

excess thromboembolic and bleeding events relative to warfarin, and current guidelines continue to reserve vitamin K antagonists for this group. Warfarin dosing accuracy therefore remains a live clinical problem, not a historical one.

This article synthesizes the pharmacogenomic literature on warfarin dosing: the genetic basis of the dose-variability problem, the algorithms built to exploit that genetic information, the randomized controlled trials that tested whether genotype-guided dosing actually changes clinical anticoagulation control and outcomes, the specific and uncomfortable finding that the benefit of two-gene genotyping is not uniform across ancestry groups, and the practical questions of cost, turnaround time, and implementation that determine whether any of this reaches a patient's bedside. We close with what we see as the genuinely open questions -- expanded genetic panels, point-of-care testing, and the shrinking but persistent population for whom this question still matters clinically.

2. Warfarin Pharmacology and the Genetic Basis of Dose Variability

Warfarin acts by inhibiting vitamin K epoxide reductase complex subunit 1 (VKORC1), the enzyme that recycles oxidized vitamin K back to its reduced form, which is required as a cofactor for the post-translational carboxylation of several clotting factors (II, VII, IX, and X) in the liver. Without that recycling step, the liver continues to synthesize these factors but in a functionally impaired, under-carboxylated form, and the net anticoagulant effect of warfarin therapy reflects the balance between the drug's inhibition of VKORC1 and the ongoing clearance of already-carboxylated clotting factors already in circulation, which is why warfarin's anticoagulant effect takes several days to become fully established after a dose change. The gene encoding this target, VKORC1, was identified independently and almost simultaneously by two groups in 2004, both of whom located it by studying families and rat populations with hereditary warfarin resistance -- a discovery that immediately reframed decades of empirical dose variability as a tractable genetic question [2,3]. A common promoter-region haplotype in VKORC1 (tagged by the single-nucleotide polymorphism rs9923231) reduces the gene's transcription and therefore the amount of target enzyme available, meaning that carriers require substantially lower

warfarin doses to achieve the same degree of anticoagulation; Rieder and colleagues showed that this VKORC1 haplotype effect alone explained a large share of the difference in average warfarin dose between Asian, European, and African-descent populations observed in earlier clinical pharmacology studies, well before the polymorphism itself had been identified [4].

The second major genetic determinant acts on the pharmacokinetic side of the problem. Warfarin is metabolized predominantly by the hepatic cytochrome P450 enzyme CYP2C9, and the two most common reduced-function variant alleles, CYP2C9² and 3, slow this clearance, prolonging the drug's half-life and increasing exposure at any given dose. Aithal and colleagues were among the first to connect these variants directly to clinical risk, reporting in 1999 that patients carrying CYP2C9² or 3 required lower maintenance doses and, more strikingly, experienced a higher rate of serious or life-threatening bleeding complications and a higher rate of over-anticoagulation episodes during the early weeks of therapy, when dosing decisions are least informed by accumulated INR data [5]. A subsequent HuGENet systematic review and meta-analysis by Sanderson, Emery, and Higgins pooled the growing body of CYP2C9 genotype-dose studies and confirmed the pattern was consistent across cohorts: variant carriers required meaningfully lower doses, took longer to reach a stable dose, and experienced excess bleeding risk, particularly during initiation [6]. Reduced-function CYP2C9 alleles are not evenly distributed across populations, which turns out to matter a great deal for how well a genotyping panel performs in different patient groups; CYP2C9² and 3 are common in individuals of European ancestry but rare in individuals of African ancestry, in whom other, less commonly tested reduced-function alleles -- CYP2C9⁵, 6, 8, and 11 -- are more prevalent. Scott and colleagues specifically documented that CYP2C9⁸, *an allele essentially absent from European-ancestry cohorts, is carried by a meaningful minority of African-American individuals and independently predicts lower warfarin dose requirement, a finding with direct consequences for any dosing algorithm that only screens for 2 and *3* [7].

A third gene, CYP4F2, which encodes an enzyme involved in vitamin K oxidation and turnover rather than warfarin metabolism itself, contributes a smaller but reproducible effect: carriers of the common CYP4F2

variant (rs2108622) tend to require modestly higher warfarin doses, an effect roughly an order of magnitude smaller than the CYP2C9 and VKORC1 effects but large enough to improve dose-prediction models when added [8]. Taken together, CYP2C9, VKORC1, and CYP4F2 give warfarin an unusually complete, and unusually early-characterized, genetic map of its own dose-response variability -- which is precisely what made it the drug on which the pharmacogenomics field chose to test whether any of this mechanistic knowledge could be translated into an algorithm that changes how doctors actually prescribe.

Non-Genetic Contributors to Dose Variability

Genetics is not the whole story, and no pharmacogenomic dosing algorithm has ever claimed otherwise; the IWPC and CPIC frameworks both combine genotype with clinical covariates precisely because genetic variants explain a large share, not all, of dose variability [9]. Age is one of the strongest non-genetic predictors, with older patients generally requiring lower maintenance doses as hepatic clearance and vitamin K turnover both decline; body size, captured in most algorithms as body surface area or weight, scales dose requirement in the expected direction. Drug interactions matter enormously and can, in an individual patient, swamp a favorable genotype: amiodarone, itself metabolized through overlapping cytochrome pathways, reliably lowers warfarin dose requirement and is explicitly included as a covariate in the IWPC algorithm for exactly this reason, while enzyme-inducing anticonvulsants and rifampin can push requirements sharply higher. Dietary vitamin K intake, mediated through leafy green vegetables and certain oils, shifts the equilibrium the drug is trying to hold in the opposite direction from most drug interactions, and abrupt changes in diet are a well-recognized, entirely non-genetic cause of INR instability in patients who were previously stable on a given dose. None of this diminishes the genetic contribution; it is the reason dosing algorithms are multivariable models rather than genotype-only lookup tables, and it is also why even a perfect genotype-guided starting dose still requires the same INR-monitoring infrastructure that clinical dosing has always relied on -- pharmacogenomic screening changes where a patient starts, not whether their anticoagulation still needs to be watched.

3. Pharmacogenetic Dosing Algorithms

The translational step from "these genes affect warfarin dose" to "here is a formula a clinician can use" required pooling enough patients, across enough sites and ancestries, to fit a stable multivariable model. The International Warfarin Pharmacogenetics Consortium (IWPC) assembled data on more than 4,000 patients from sites on four continents and derived and validated a pharmacogenetic dosing algorithm that combines CYP2C9 and VKORC1 genotype with clinical variables -- age, body surface area, target INR, amiodarone use, smoking status, and race -- to predict a stable therapeutic weekly dose, publishing the algorithm alongside a comparison, purely clinical algorithm that used the same variables minus genotype [9]. A subsequent independent validation study extending the IWPC framework to incorporate CYP4F2 and pooled rare CYP2C9 variants reported that the pharmacogenetic algorithm explained approximately 50% of the variability in warfarin dose requirement, compared with roughly 22% for the clinical-only algorithm, and that adding genotype increased the proportion of patients whose predicted dose fell within 1 mg/day of their actual therapeutic dose from 54% to 63% [8]. This is the central empirical claim underlying the entire pharmacogenomic-dosing enterprise: genotype adds real, reproducible predictive information on top of the clinical variables a prescriber already has, roughly doubling the explained variance in dose requirement.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) translated this evidence into an actionable clinical guideline, first published in 2011 and updated in 2017, providing a genotype-to-dose lookup that clinicians and pharmacists can apply directly rather than needing to run a regression themselves, alongside explicit recommendations on how to weight genotype information against clinical factors when the two are in tension [10,11]. The CPIC guideline sits alongside similar recommendations from the U.S. Food and Drug Administration, which since 2007 has included a pharmacogenomic dosing table in the warfarin product label, listing expected therapeutic dose ranges stratified by combined CYP2C9 and VKORC1 genotype. That the regulator, and not only the research consortium, considered the evidence sufficient to modify prescribing information is itself a data point about how mature this particular gene-drug pair was judged to be relative to most other pharmacogenomic associations at the time.

An early Rapid-ACCE evidence review commissioned to formally assess whether CYP2C9 and VKORC1 testing met the analytic validity, clinical validity, clinical utility, and associated ethical, legal, and social implications criteria used for evaluating genetic tests concluded that analytic and clinical validity were well established, but that clinical utility -- whether testing actually improved patient outcomes, rather than simply predicting dose more accurately -- required direct evidence from randomized trials rather than being inferred from the strength of the genotype-dose association alone [12]. That distinction -- a dosing algorithm that predicts the right dose more accurately is not automatically an intervention that improves anticoagulation control or reduces adverse events -- turned out to be exactly the right thing to be cautious about, because it is where the subsequent trial evidence diverged.

4. Randomized Controlled Trial Evidence for Genotype-Guided Dosing

The move from validated dosing algorithm to demonstrated clinical benefit required randomized trials comparing genotype-guided initiation against a standard-of-care comparator, and several large, well-conducted trials delivered results that did not all point the same direction, which is itself an important part of the evidence base rather than a nuisance to explain away. The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) warfarin trial randomized 455 patients starting warfarin for atrial fibrillation or venous thromboembolism across UK and Swedish centers to genotype-guided or standard dosing and found that the genotype-guided group spent significantly more time in the therapeutic INR range over the first 12 weeks of therapy -- 67.4% versus 60.3% ($p < 0.001$) -- reached a stable therapeutic INR faster (a median of 21 versus 29 days), and had fewer episodes of markedly supratherapeutic INR of 4.0 or above (27.0% versus 36.6%) [13]. A companion EU-PACT trial conducted in the Netherlands and Belgium, using the same genotype-guided approach applied to acenocoumarol and phenprocoumon -- the vitamin K antagonists used in continental Europe rather than warfarin itself, but sharing the same CYP2C9/VKORC1 pharmacogenetic mechanism -- similarly found that genotype-guided dosing reduced the proportion of out-of-range INR measurements during the initiation period relative to standard dosing [14].

Table 1: The major randomized controlled trials of genotype-guided warfarin dosing, their populations and comparators, and the primary result each reported [13,14,15,16].

Trial	Population / Comparator	Primary Outcome	Result
EU-PACT warfarin	AF/VTE patients (UK, Sweden); genotype-guided vs standard dosing	% time in therapeutic INR range, weeks 1-12	67.4% vs 60.3% (p<0.001)
EU-PACT acenocoumarol/phenprocoumon	AF/VTE patients (Netherlands, Belgium); genotype-guided vs standard dosing	% out-of-range INR, initiation period	Reduced with genotype-guided dosing
COAG	AF/VTE patients (USA); genotype-guided vs clinical-algorithm dosing	% time in therapeutic INR range, weeks 1-4	45.2% vs 45.4% overall (p=0.91); 35.2% vs 43.5% in African-American subgroup (p=0.01)
GIFT	Hip/knee arthroplasty patients (USA); genotype-guided vs clinical-algorithm dosing	Composite: major bleeding, INR≥4, VTE, or death	10.8% vs 14.7% (relative rate 0.73, p=0.02)

The Clarification of Optimal Anticoagulation through Genetics (COAG) trial, a larger, US-based, multicenter trial of 1,015 patients, tested a closely related but not identical question -- genotype-guided dosing against a clinical-algorithm-guided comparator, rather than against a simple fixed-dose or purely empirical standard of care -- and found no overall difference in time in therapeutic range over the first four weeks: 45.2% in the genotype-guided arm versus 45.4% in the clinical-algorithm arm (p=0.91) [15]. The comparator matters enormously for interpreting this null result: COAG was testing whether genotype information adds value on top of an already-good clinical algorithm, a higher bar than EU-PACT's comparison against unstructured standard care, and under that stricter test genotype-guided dosing did not clear the bar in the trial population as a whole. The Genetics Informatics Trial (GIFT) took the question to a different population -- 1,650 patients starting warfarin after elective hip or knee arthroplasty, a setting with a well-defined, time-limited anticoagulation course and a composite outcome (major bleeding, INR of 4 or higher, symptomatic venous thromboembolism, or death) that captured both directions of dosing error -- and found that genotype-guided dosing significantly reduced the composite outcome, 10.8% versus 14.7% in the clinically-guided group (relative rate 0.73, 95% CI 0.56-0.95, p=0.02), a benefit driven mainly by fewer episodes of markedly elevated INR rather than by a

reduction in bleeding or thrombosis events individually [16].

Reconciling EU-PACT's positive result, COAG's null result, and GIFT's positive result on a clinical-event composite is not simply a matter of picking a side; systematic reviews that pool the accumulated trial evidence give the more useful answer. Tse and colleagues' 2018 meta-analysis of randomized controlled trials found that genotype-guided dosing was associated with a modest but statistically significant improvement in time in therapeutic range and a reduction in the proportion of patients with an INR of 4 or above, without a clear, consistent effect on major bleeding or thromboembolic events across trials [17]. Wang and colleagues' 2022 meta-analysis of 27 randomized controlled trials reached a similar overall conclusion: genotype-guided dosing modestly but consistently improved process measures of anticoagulation control relative to non-genotype-guided strategies, while effects on hard clinical outcomes -- major bleeding, thromboembolism, and mortality -- were smaller and less consistently significant across the pooled trials [18]. Read together, the trial and meta-analytic evidence supports a fairly specific and appropriately modest claim: pharmacogenomic screening reliably improves how quickly and how precisely a patient's anticoagulation is controlled during warfarin initiation, and that improvement translates into a measurable reduction in clinically meaningful over-anticoagulation events in at least some populations and against at least some comparators, but it is not a uniform, unconditional reduction in bleeding or thrombosis across every trial design and every population studied.

5. Ancestry, Health Equity, and the Limits of Two-Gene Algorithms

The most clinically important qualification to the trial evidence is not a matter of statistical power but of who the two-gene testing panel was built around. A pre-specified subgroup analysis in the COAG trial found a significant interaction between treatment arm and self-identified race (p=0.03): among African-American participants, genotype-guided dosing performed worse than clinical-algorithm dosing, with a time in therapeutic range of 35.2% versus 43.5% (p=0.01), while non-African-American participants showed no meaningful difference between the two dosing

strategies. The COAG investigators attributed this reversal to exactly the population-genetics point raised earlier: CYP2C9² and 3, the two variant alleles included in both the IWPC and COAG genotyping panels, are uncommon in individuals of African ancestry, in whom other reduced-function CYP2C9 alleles -- 5, 6, 8, and 11 -- are more prevalent and were not captured by the panel used, so the genotype-guided algorithm was, in effect, running on incomplete genetic information for a substantial fraction of that subgroup while still directing dosing decisions with the same confidence as it did for patients whose relevant variants it had actually measured.

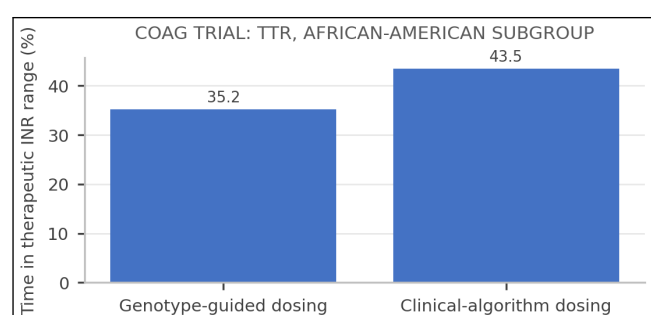


Figure 1: Time in therapeutic range achieved with genotype-guided versus clinical-algorithm warfarin dosing in the COAG trial's pre-specified African-American subgroup, where the two-allele CYP2C9/VKORC1 panel underperformed a purely clinical algorithm ($p=0.01$ for the difference) -- the finding underlying this article's discussion of ancestry gaps in genotyping panel coverage [15].

This finding did not emerge from a single trial in isolation. Price's commentary on warfarin pharmacogenomics and African ancestry situates the COAG subgroup result within a broader literature showing that dosing algorithms derived predominantly from European- and Asian-ancestry cohorts systematically underperform, and can actively mislead, when applied without modification to patients of African ancestry, precisely because the genetic architecture of warfarin sensitivity is not identical across ancestry groups even though the two core genes involved are the same [19]. Scott and colleagues' earlier documentation of CYP2C9's prevalence specifically in African-American individuals, and its independent association with lower dose requirement, is the underlying mechanistic explanation rather than a separate finding [7]. This is a genuinely uncomfortable result for the field to sit with: the two-gene test that improved outcomes in EU-PACT's largely European-ancestry cohort and in GIFT's arthroplasty population appears, in the one large US trial that formally tested for a race interaction and had adequate numbers to detect one, to have caused harm in

a specific ancestry subgroup relative to a purely clinical algorithm, not because pharmacogenomics as a principle is wrong but because the specific panel tested was incomplete for that population. The practical implication is not that genotype-guided dosing should be abandoned in patients of African ancestry, but that a genotyping panel limited to CYP2C9²/3 and VKORC1 is an inadequate test in that population specifically, and expanded panels that include 5, 6, 8, and *11 are a genuine, unmet need rather than a marginal refinement, a point the CPIC guideline itself acknowledges by recommending expanded allele testing where population ancestry make the additional alleles relevant [11].

6. Implementation, Cost, and Point-of-Care Testing

Even a test with demonstrated clinical utility in the right population does not implement itself, and warfarin pharmacogenomics has run into the same adoption friction that affects clinical pharmacogenomics broadly: genotyping results are not always available before the first dose must be given, laboratory turnaround time historically ran from days to over a week for send-out genotyping, and clinicians have to trust and act on a result that arrives in an unfamiliar format from a laboratory system many were not trained to interpret. Kanegusuku and colleagues' review of implementation challenges in clinical pharmacogenomics more broadly identifies exactly these obstacles -- physician awareness gaps, unclear or overly technical result reporting, and inconsistent reimbursement -- as recurring barriers across gene-drug pairs, not specific to warfarin, which suggests the adoption problem is as much a systems and workflow problem as a genetics problem [20]. Huang and Gamazon's implementation framework makes a related point at a higher level: translating a validated pharmacogenomic association into routine clinical use requires pre-emptive, panel-based genotyping built into the electronic health record rather than reactive, single-gene ordering at the point of a specific prescribing decision, because reactive testing is almost always too slow to inform an urgent first dose [21]. For warfarin specifically, where the first dose is frequently needed within hours of a clinical decision to anticoagulate, this timing mismatch is not a minor inconvenience but a central obstacle to any of the trial results translating into everyday practice, and it is the direct motivation behind point-of-care and

rapid-turnaround genotyping platforms that return a CYP2C9/VKORC1 result within a single clinic visit rather than after the dosing decision has already been made empirically.

Turnaround time deserves particular attention because it interacts with warfarin's clinical timeline in a way that is easy to understate in the abstract. A patient starting warfarin for a new venous thromboembolism or newly diagnosed atrial fibrillation typically needs a first dose the same day the decision to anticoagulate is made; a genotyping result that arrives 3 to 5 days later, which was a realistic turnaround for the send-out laboratory testing used in the earlier era of this literature, cannot inform that first dose at all and can only adjust the second or third dose onward, which is a meaningfully weaker intervention than the trials synthesized here were designed to test. This is precisely the gap that point-of-care and rapid-turnaround genotyping platforms, capable of returning a CYP2C9/VKORC1 result within one to two hours from a buccal swab or fingerstick sample, are intended to close, and their appeal is less about novelty than about actually matching the pharmacogenomic intervention to the clinical decision window it is supposed to inform. Whether same-day point-of-care genotyping produces the same magnitude of benefit seen in trials that used slower laboratory turnaround is a question the existing major outcome trials, which relied on conventional laboratory genotyping, are not well positioned to answer on their own, and it is one of the clearer places where the technology has outpaced the outcome evidence built specifically around it.

Cost-effectiveness analyses have generally been more favorable to genotype-guided dosing than the mixed clinical-outcome trial evidence might suggest on its own, in large part because the genotyping cost is a one-time expense weighed against a chronic condition's cumulative bleeding and stroke risk over years of anticoagulation. Patrick, Avorn, and Choudhry's model of genotype-guided warfarin dosing in patients with atrial fibrillation estimated that the approach could be cost-effective under a range of assumptions about testing cost and the size of the clinical benefit, though the estimate was sensitive to exactly how much benefit was assumed, underscoring that a cost-effectiveness case for pharmacogenomic warfarin dosing is not independent of the same clinical-trial uncertainty

already described above [22]. A later analysis modeling the EU-PACT trial's own results in UK and Swedish health-system contexts similarly found genotype-guided dosing to be a cost-effective, and in some scenarios cost-saving, strategy once the reduction in bleeding-related hospitalizations, however modest, was accounted for [23]. Efforts to make genotype information usable beyond the specific two-gene panels validated in the major trials -- such as Shahabi and colleagues' expanded pharmacogenomic warfarin dosing table, built to generalize dosing guidance to genotype combinations not well represented in the original derivation cohorts -- reflect a broader push toward making the pharmacogenomic dosing evidence base more complete and more portable across populations and testing platforms, complementing the CPIC guideline rather than replacing it [24]. Ragia and Manolopoulos's review of the past decade of anticoagulation pharmacogenomics situates warfarin dosing within this wider trajectory: a field that started with a single, well-characterized gene-drug pair and has since had to reckon with population diversity, implementation logistics, and a shrinking but still clinically important population of patients for whom the question has not become moot [25].

7. Open Challenges

Where Warfarin Pharmacogenomics Still Matters Clinically

It is worth being explicit about who this evidence base is actually for, because the population has narrowed considerably since the major trials synthesized here were designed and enrolled. Mechanical heart valve recipients are the clearest remaining indication: a randomized trial of dabigatran against warfarin in this population was stopped early for an excess of both thromboembolic and bleeding events in the dabigatran arm, and current cardiology and hematology society guidance continues to specify a vitamin K antagonist, not a direct oral anticoagulant, for anyone with a mechanical valve. Patients with antiphospholipid syndrome and high-risk clot burden represent a second population where trial evidence for direct oral anticoagulants has been unfavorable enough that warfarin remains standard of care. A third, less clinical and more structural population consists of patients for whom a direct oral anticoagulant's cost, even after generic entry, remains a genuine access barrier relative to warfarin's substantially lower price and broader

insurance coverage in many health systems, particularly outside high-income countries. None of these populations are shrinking toward zero, and mechanical valve replacement in particular is not a procedure that is going away; if anything, an aging population undergoing valve replacement means the absolute number of patients who need accurate warfarin dosing may remain substantial even as warfarin's share of all anticoagulant prescriptions continues to decline. This is the practical argument for why the ancestry-specific gap in genotyping panel coverage discussed above is not a historical footnote to be resolved at leisure: the patients for whom warfarin pharmacogenomics is most clinically relevant going forward are, almost by definition, exactly the patients for whom getting the first dose right matters most, because they frequently have the least room for either an undertreated clot or an overtreated bleed.

Several gaps in this evidence base are worth stating plainly. First, the ancestry-specific finding from COAG has not, to our knowledge, been definitively resolved by a subsequent trial specifically testing an expanded, ancestry-inclusive genotyping panel against the standard two-allele panel in a population enriched for African ancestry; the mechanistic explanation is well supported, but the direct trial evidence that an expanded panel closes the observed gap is thinner than the evidence establishing that the gap exists in the first place. Second, the field's randomized trials, taken individually, tested genotype-guided dosing against different comparators (standard care in EU-PACT, a structured clinical algorithm in COAG, a clinical algorithm in a surgical population in GIFT), which is scientifically appropriate but makes any single trial's result a partial answer to the underlying clinical question rather than a complete one, and it means clinicians reading a single trial in isolation risk drawing the wrong general conclusion from a result that was actually specific to that trial's comparator and population. Third, point-of-care and rapid-turnaround genotyping technology has matured considerably, but the outcome evidence for it specifically -- as opposed to for genotype-guided dosing using conventional, slower-turnaround laboratory genotyping -- is comparatively underdeveloped relative to how central rapid turnaround is to warfarin's own clinical timeline; most of the major outcome trials synthesized here used laboratory genotyping with turnaround measured in days, which is a reasonable design for a trial but does not

fully answer whether a same-day point-of-care result changes outcomes in exactly the acute-initiation window where dosing errors are most consequential. Fourth, cost-effectiveness estimates remain sensitive to local genotyping costs and reimbursement structures that vary substantially by health system and have changed considerably since the earliest models were published, so a cost-effectiveness conclusion reached for one country's health system in one year should not be assumed to generalize.

Finally, warfarin's shrinking but persistent role in specific populations -- mechanical heart valves, antiphospholipid syndrome, and patients for whom direct oral anticoagulants are unaffordable or contraindicated -- means this is not a closed research question simply because warfarin's overall prescription share has declined. If anything, as the overall population on warfarin narrows toward patients with fewer alternative options, the argument for getting dosing right the first time, and for making sure the genotyping panel used actually reflects that narrower population's genetic diversity, becomes more rather than less important.

8. Conclusion

The literature synthesized here supports a specific, evidence-grounded position on pharmacogenomic warfarin dosing rather than either the optimistic version ("genotyping solves warfarin dosing") or the dismissive version ("the trials were mixed, so it doesn't work") that both circulate in less careful summaries of this evidence. CYP2C9, VKORC1, and to a lesser degree CYP4F2 genuinely explain a large share of inter-patient warfarin dose variability, roughly doubling the variance explained relative to clinical variables alone [9,8], and validated dosing algorithms built on that genetic information are now embedded in a formal clinical guideline and in the FDA product label itself [10,11]. Randomized trials consistently show that genotype-guided dosing improves process measures of anticoagulation control -- time in therapeutic range, time to stable dosing, and the frequency of markedly supratherapeutic INR values -- relative to standard or clinically-guided dosing, with the clearest clinical-event benefit demonstrated in a surgical population with a well-defined anticoagulation course [13,16,17,18]. Set against that, the COAG trial's null overall result and its specific finding of harm in an African-American subgroup are not evidence against pharmacogenomic screening as a principle, but direct

evidence that the specific two-allele CYP2C9 panel used in the major trials is an incomplete test for a genetically diverse patient population, with expanded-panel testing an identified but not yet fully trial-validated solution [15,19,7]. Implementation and cost remain real, solvable, and only partially solved obstacles rather than reasons to set the approach aside [20,21,23]. Warfarin pharmacogenomics, in short, is a mature enough evidence base to guide practice for the population it was built and tested on, and honest enough about its own limits, most importantly the ancestry gap in panel coverage, to identify exactly where the next round of trial evidence needs to go.

9. References

1. Navar, A.M., Kolkailah, A.A., Overton, R., Shah, N.P., Rousseau, J.F., Flaker, G.C., Pignone, M.P., Peterson, E.D. (2022) Trends in Oral Anticoagulant Use Among 436,864 Patients with Atrial Fibrillation in Community Practice, 2011 to 2020. *Journal of the American Heart Association*, 11(22): e026723. DOI: [10.1161/JAHA.122.026723](https://doi.org/10.1161/JAHA.122.026723)
2. Rost, S., Fregin, A., Ivaskevicius, V., et al. (2004) Mutations in VKORC1 Cause Warfarin Resistance and Multiple Coagulation Factor Deficiency Type 2. *Nature*, 427(6974): 537-541. DOI: [10.1038/nature02214](https://doi.org/10.1038/nature02214)
3. Li, T., Chang, C.-Y., Jin, D.-Y., Lin, P.-J., Khvorova, A., Stafford, D.W. (2004) Identification of the Gene for Vitamin K Epoxide Reductase. *Nature*, 427(6974): 541-544. DOI: [10.1038/nature02254](https://doi.org/10.1038/nature02254)
4. Rieder, M.J., Reiner, A.P., Gage, B.F., et al. (2005) Effect of VKORC1 Haplotypes on Transcriptional Regulation and Warfarin Dose. *New England Journal of Medicine*, 352(22): 2285-2293. DOI: [10.1056/NEJMoa044503](https://doi.org/10.1056/NEJMoa044503)
5. Aithal, G.P., Day, C.P., Kesteven, P.J.L., Daly, A.K. (1999) Association of Polymorphisms in the Cytochrome P450 CYP2C9 with Warfarin Dose Requirement and Risk of Bleeding Complications. *The Lancet*, 353(9154): 717-719. DOI: [10.1016/S0140-6736\(98\)04474-2](https://doi.org/10.1016/S0140-6736(98)04474-2)
6. Sanderson, S., Emery, J., Higgins, J. (2005) CYP2C9 Gene Variants, Drug Dose, and Bleeding Risk in Warfarin-Treated Patients: A HuGenet Systematic Review and Meta-Analysis. *Genetics in Medicine*, 7(2): 97-104. DOI: [10.1097/01.GIM.0000153664.65759.CF](https://doi.org/10.1097/01.GIM.0000153664.65759.CF)
7. Scott, S.A., Jaremko, M., Lubitz, S.A., Kornreich, R., Halperin, J.L., Desnick, R.J. (2009) CYP2C9*8 is Prevalent Among African-Americans: Implications for Pharmacogenetic Dosing. *Pharmacogenomics*, 10(8): 1243-1255. DOI: [10.2217/pgs.09.71](https://doi.org/10.2217/pgs.09.71)
8. Sagriya, H., Berube, C., Wen, A., Ramakrishnan, R., Mir, A., Hamilton, A., Altman, R.B. (2010) Extending and Evaluating a Warfarin Dosing Algorithm that Includes CYP4F2 and Pooled Rare Variants of CYP2C9. *Pharmacogenetics and Genomics*, 20(7): 407-413. DOI: [10.1097/FPC.0b013e328338bac2](https://doi.org/10.1097/FPC.0b013e328338bac2)
9. International Warfarin Pharmacogenetics Consortium (Klein TE, Altman RB, Eriksson N, et al.) (2009) Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data. *New England Journal of Medicine*, 360(8): 753-764. DOI: [10.1056/NEJMoa0809329](https://doi.org/10.1056/NEJMoa0809329)
10. Johnson, J.A., Gong, L., Whirl-Carrillo, M., et al. (2011) Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 Genotypes and Warfarin Dosing. *Clinical Pharmacology & Therapeutics*, 90(4): 625-629. DOI: [10.1038/clpt.2011.185](https://doi.org/10.1038/clpt.2011.185)
11. Johnson, J.A., Caudle, K.E., Gong, L., et al. (2017) Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. *Clinical Pharmacology & Therapeutics*, 102(3): 397-404. DOI: [10.1002/cpt.668](https://doi.org/10.1002/cpt.668)
12. McClain, M.R., Palomaki, G.E., Piper, M., Haddow, J.E. (2008) A Rapid-ACCE Review of CYP2C9 and VKORC1 Alleles Testing to Inform Warfarin Dosing in Adults at Elevated Risk for Thrombotic Events to Avoid Serious Bleeding. *Genetics in Medicine*, 10(2): 89-98. DOI: [10.1097/GIM.0b013e31815bf924](https://doi.org/10.1097/GIM.0b013e31815bf924)
13. Pirmohamed, M., Burnside, G., Eriksson, N., et al. (2013) A Randomized Trial of Genotype-Guided Dosing of Warfarin. *New England Journal of Medicine*, 369(24): 2294-2303. DOI: [10.1056/NEJMoa1311386](https://doi.org/10.1056/NEJMoa1311386)
14. Verhoef, T.I., Ragia, G., de Boer, A., et al. (2013) A Randomized Trial of Genotype-Guided Dosing of Acenocoumarol and Phenprocoumon. *New England Journal of Medicine*, 369(24): 2304-2312. DOI: [10.1056/NEJMoa1311388](https://doi.org/10.1056/NEJMoa1311388)
15. Kimmel, S.E., French, B., Kasner, S.E., et al. (2013) A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing. *New England Journal of Medicine*, 369(24): 2283-2293. DOI: [10.1056/NEJMoa1310669](https://doi.org/10.1056/NEJMoa1310669)
16. Gage, B.F., Bass, A.R., Lin, H., et al. (2017) Effect of Genotype-Guided Warfarin Dosing on Clinical Events and Anticoagulation Control Among Patients Undergoing Hip or Knee Arthroplasty: The GIFT Randomized Clinical Trial. *JAMA*, 318(12): 1115-1124. DOI: [10.1001/jama.2017.11469](https://doi.org/10.1001/jama.2017.11469)
17. Tse, G., Gong, M., Li, G., et al. (2018) Genotype-Guided Warfarin Dosing vs. Conventional Dosing Strategies: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *British Journal of Clinical Pharmacology*, 84(9): 1868-1882. DOI: [10.1111/bcp.13621](https://doi.org/10.1111/bcp.13621)
18. Wang, X., Tang, B., Zhou, M., Liu, L., Feng, X., Wang, X., Qiu, K.

- (2022) Efficacy and Safety of Genotype-Guided Warfarin Dosing versus Non-Genotype-Guided Warfarin Dosing Strategies: A Systematic Review and Meta-Analysis of 27 Randomized Controlled Trials. *Thrombosis Research*, 210: 42-52. DOI: [10.1016/j.thromres.2021.12.023](https://doi.org/10.1016/j.thromres.2021.12.023)
19. Price, E.T. (2015) Warfarin Pharmacogenomics and African Ancestry. *Blood*, 126(4): 434-436. DOI: [10.1182/blood-2015-06-649509](https://doi.org/10.1182/blood-2015-06-649509)
 20. Kanegusuku, A.G., Chan, C.W., Thoburn, C.A., van Wijk, X.M.R., Tang, N.Y. (2025) Challenges and Considerations in Implementing Clinical Pharmacogenomics. *Journal of Laboratory and Precision Medicine*, 10(1): 2. DOI: [10.21037/jlpm-24-36](https://doi.org/10.21037/jlpm-24-36)
 21. Huang, R.S., Gamazon, E.R. (2013) Translating Pharmacogenomics Discoveries into the Clinic: An Implementation Framework. *Genome Medicine*, 5(10): 94. DOI: [10.1186/gm497](https://doi.org/10.1186/gm497)
 22. Patrick, A.R., Avorn, J., Choudhry, N.K. (2009) Cost-Effectiveness of Genotype-Guided Warfarin Dosing for Patients with Atrial Fibrillation. *Circulation: Cardiovascular Quality and Outcomes*, 2(5): 429-436. DOI: [10.1161/CIRCOUTCOMES.108.808592](https://doi.org/10.1161/CIRCOUTCOMES.108.808592)
 23. Verhoef, T.I., Redekop, W.K., Langenskiold, S., et al. (2016) Cost-Effectiveness of Pharmacogenetic-Guided Dosing of Warfarin in the United Kingdom and Sweden. *The Pharmacogenomics Journal*, 16(5): 478-484. DOI: [10.1038/tpj.2016.41](https://doi.org/10.1038/tpj.2016.41)
 24. Shahabi, P., Scheinfeldt, L.B., Lynch, D.E., et al. (2016) An Expanded Pharmacogenomics Warfarin Dosing Table with Utility in Generalised Dosing Guidance. *Thrombosis and Haemostasis*, 116(2): 1-12. DOI: [10.1160/TH15-12-0955](https://doi.org/10.1160/TH15-12-0955)
 25. Ragia, G., Manolopoulos, V.G. (2019) Pharmacogenomics of Anticoagulation Therapy: The Last 10 Years. *Pharmacogenomics*, 20(16): 1113-1117. DOI: [10.2217/pgs-2019-0149](https://doi.org/10.2217/pgs-2019-0149)

10. Declarations

Funding

This literature synthesis did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare no competing interests relevant to the content of this article.

Data Availability Statement

No new data were generated or analysed for this article, as it is a synthesis of previously published literature. All studies discussed are cited in the reference list; readers should consult the original publications for their underlying data and code availability statements.

Ethical Approval

Not applicable. This article is a literature synthesis and did not involve the recruitment of human participants, animal subjects, or the collection of primary clinical data.

Citation: Kenzhebekov A, Bekturov G, Serikbayev A. "Clinical Impact of Pharmacogenomic Screening on Warfarin Dosing Accuracy." *J Clin Pharm Res* (2026): 001-010 doi: [10.5281/zenodo.22849402](https://doi.org/10.5281/zenodo.22849402)