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Review Article

UNCHARTED GENETIC RISKS IN IDIOPATHIC DEEP VEIN THROMBOSIS: F2, PROC, F9 VARIANTS AND ACCESSIBLE PRECISION PATHWAYS

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ABSTRACT

Idiopathic deep vein thrombosis (DVT) remains difficult to manage, as recurrence risk is high even after appropriate anticoagulation. Current risk assessment models depend mostly on clinical factors and oversimplify hereditary thrombophilia, grouping it as one category. Recent studies show that rare and population-specific genetic variants, particularly in F2, PROC, and F9, play a significant role in hypercoagulability among patients classified as having unprovoked DVT. Notably, rare PROC variants are increasingly recognized as major risk factors, with strong evidence from sequencing studies and functional analyses. In contrast, while F9 gain-of-function variants are biologically plausible contributors, direct epidemiologic evidence for their link to idiopathic DVT is still weak. Standard diagnostic algorithms estimate event probability but overlook genetic complexity, especially in underrepresented Asian and resource-limited populations. A stepwise approach that combines clinical triage, structured diagnostics, and targeted gene sequencing could improve risk assessment and be feasible for tertiary hospitals with limited resources. Key future steps include broadening genetic research to diverse populations and developing scalable precision care models for thrombosis prevention and management.

Keywords: Protein C, Factor, Prothrombin, Thrombophilia, Genetic Sequencing.

INTRODUCTION

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a leading cause of preventable morbidity and mortality worldwide. Global estimates indicate that thrombosis-related disorders account for a substantial proportion of cardiovascular deaths, with VTE incidence increasing sharply with age and strongly associated with hospitalization, malignancy, surgery, trauma, hormonal therapy, and immobilization (Raskob G. E, 2014). A substantial proportion of venous thromboembolism events occur in the absence of identifiable transient risk factors. Idiopathic or unprovoked DVT refers to thrombosis developing without major provoking conditions such as surgery, trauma, or active malignancy. These patients carry a higher long-term recurrence risk compared with those with provoked events. Observational data indicate that the risk of recurrence increases progressively after anticoagulation cessation, reaching approximately 25% at 5 years and 30-40% at 10 years (Linnemann B, 2024). The continuous threat of danger suggests that hidden prothrombotic forces persist after the initial incident. The current diagnostic algorithms, which use Wells-based probability assessments together with structured D-dimer pathways, aim to determine the likelihood of acute events rather than identifying the underlying mechanisms that cause these events (Linnemann B, 2024). “Hereditary thrombophilia” exists as a dualistic genetic marker that doctors use to assess patients without understanding their genomic complexities. Consequently, rare or population-specific genetic variants may remain undetected in patients labelled as having idiopathic DVT.

RESEARCH STRATEGY AND METHODS

A structured narrative review was conducted to synthesise evidence regarding rare and population-specific genetic contributors to idiopathic deep vein thrombosis, with

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emphasis on F2, PROC, and F9 variants and their relevance to resource-limited tertiary care settings. Literature searches were performed using PubMed/MEDLINE, Scopus, Google Scholar, and PubMed Central. Search terms were combined using Boolean operators and included: "idiopathic DVT," "unprovoked venous thromboembolism," "F2 G20210A," "prothrombin mutation," "PROC mutation," "protein C deficiency," "F9 variant," "factor IX thrombosis," "rare thrombophilia," "gene burden VTE," "polygenic risk score venous thromboembolism," "Asian thrombophilia," and "precision medicine resource-limited thrombophilia." Original research articles, cohort studies, genome-wide and targeted sequencing analyses, mechanistic investigations, guideline statements, and relevant review articles published between 2015 and 2026 were prioritized. Seminal earlier studies were included where foundational to the understanding of inherited thrombophilia. Studies were selected based on relevance to idiopathic or unprovoked DVT, strength of genetic association, mechanistic plausibility, and representation of diverse populations. A narrative synthesis approach was used to integrate epidemiologic, molecular, clinical, and health systems perspectives.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF IDIOPATHIC DEEP VEIN THROMBOSIS

Western populations experience a yearly incidence rate between 1 and 2 cases of venous thromboembolism which includes deep vein thrombosis and pulmonary embolism as a major cardiovascular disorder (Heit J. A, 2015, Kearon C, 2003). First-time VTE events develop in the majority of cases without any major temporary risk factors which include surgical procedures and traumatic incidents and active cancer detection. The initial presentation of unprovoked events occurs in approximately one-third to one-half of cases according to population-based data (Heit J. A, 2015, Kearon C, 2003). Older people develop VTE at higher rates yet younger patients show more unprovoked events than provoked thrombosis. First-degree relatives of affected individuals face significantly higher VTE risks according to familial aggregation studies which prove that VTE susceptibility has an inherited component (Merchant F. M, 2012). The multicausal model developed by Rosendaal explains venous thrombosis as a condition which occurs when genetic and acquired risk factors combine to surpass a specific clinical threshold (Rosendaal F. R, 1999).

Multiple genetic variants which increase VTE risk have been discovered through genome-wide association studies and meta-analyses that identify genetic loci in F5, F2, ABO and additional coagulation-related genes (Chong J. X, 2015). The typical effect size of these common variants shows a modest impact on outcomes. Natural anticoagulant deficiencies which include protein C and protein S and antithrombin present a rare inherited condition that results in significantly elevated risk levels (Lijfering W. M, 2010). Twin and family studies estimate that genetic factors may account for approximately half of overall VTE susceptibility (Merchant F. M, 2012). The process of hemostasis requires precise control of procoagulant activities and anticoagulant activities to maintain proper function. The activation of intrinsic and extrinsic coagulation pathways results in the production of thrombin which leads to the creation of fibrin while natural anticoagulant mechanisms mainly the protein C pathway antithrombin and tissue factor pathway inhibitor function to restrict excessive clot development (Rosendaal F. R, 1999). Research has shown that different ethnic groups exhibit distinct patterns of thrombophilia distribution. The mutations Factor V Leiden and F2 G20210A are present in European populations but they are absent in East Asian communities (Girard T. J,2013). The natural anticoagulant deficiencies which exist in Asian communities serve as more significant reasons for VTE according to multiple studies (Kimura R, 2012). The existing differences between populations demonstrate that researchers need to conduct thrombophilia studies according to specific ancestral heritage.

CURRENT RISK ASSESSMENT MODELS - WHERE GENETICS IS UNDERREPRESENTED

Risk prediction tools have significantly improved VTE management but are fundamentally grounded in clinical variables. The Padua Prediction Score, which was created for use with hospitalised medical patients, determines risk through its assessment of multiple medical conditions that include cancer, prior VTE, and patient immobility and thrombophilia (Barbar S, 2010). The system includes thrombophilia as a single category, but does not distinguish between mild genetic variations and severe, rare genetic mutations. The Khorana score predicts chemotherapy-associated VTE risk based on tumor type and hematologic parameters (Khorana A. A, 2005). Subsequent validation studies have demonstrated variable performance in specific cancers, including pancreatic malignancy (Van Es, N, 2017). Importantly, inherited genetic variation is not directly incorporated. Diagnostic tools such as the Revised Geneva Score and Wells criteria rely on clinical history and signs to estimate pretest probability (Le Gal G, 2006). Meta-analytic evaluations confirm their diagnostic efficiency when combined with D-dimer testing (Hendriksen J. M, 2015) and validation in trauma populations has been reported (Modi S, 2016). Nevertheless, these models assess acute likelihood rather than underlying thrombophilia. Across these frameworks, hereditary thrombophilia is oversimplified. Rare deleterious variants, gene-environment interactions, and cumulative variant burden are not captured, leaving a gap in identifying hidden genetic risk.

PATHOPHYSIOLOGIC FRAMEWORK OF HYPERCOAGULABILITY

Virchow's triad of venous stasis, endothelial injury, and hypercoagulability remains central to thrombosis biology. In cancer and chronic illness, these components interact dynamically (Leśkiewicz M, 2024). The malignant tumour process creates excessive tissue factor (TF) production,

which establishes a link between cancer-driven signalling pathways and thrombin production (Rak J, 2006). Tumours release TF, which allows them to produce fibrin while simultaneously activating platelets to boost the body's normal functions of blood clotting. Endothelial dysfunction results in the body producing more platelet activation because it generates prothrombotic signals. Chronic inflammatory conditions lead to decreased nitric oxide production in the body, which results in the loss of anticoagulant surface protection (Leśkiewicz M, 2024, Rak J, 2006). The bloodstream contains tissue factor (TF) microparticles, which establish a biological connection between body-wide inflammation and blood clot formation in specific areas. Medical research demonstrates that when TF-positive microparticles reach high concentrations, they create a connection to venous thromboembolism because intravascular TF starts thrombin production, which leads to fibrin creation (Tam C. S, 2009). The mechanism provides an explanation for how body wide procoagulant conditions result in the formation of blood clots at specific locations. The convergence of the intrinsic and extrinsic pathways on thrombin generation and fibrin formation, along with regulatory control by the protein C system, is illustrated in (Figure 1).

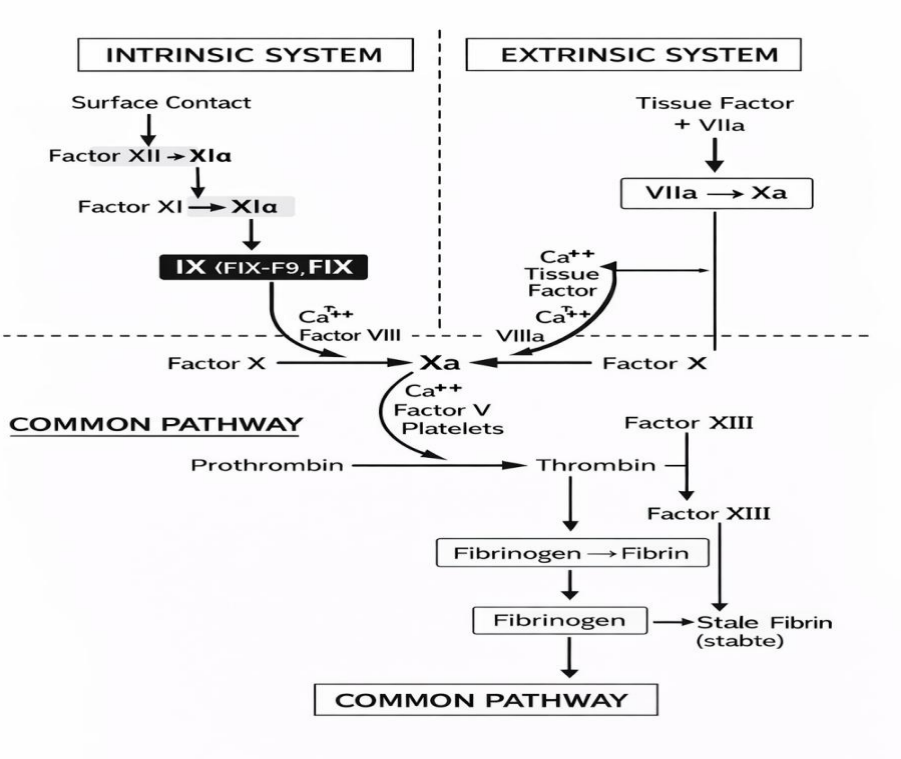

Figure 1. Schematic Representation of the Intrinsic, Extrinsic, and Common Coagulation Pathways Relevant to Idiopathic DVT

PROC VARIANTS-EMERGING HIGH-RISK GENETIC SIGNAL

The PROC gene acts as an essential genetic risk factor because it contains harmful rare variants that impact anticoagulant pathways. Patients with unprovoked VTE have shown targeted sequencing studies, which detected rare coding variants in PROC and PROCR that do not exist in control groups (Wu C, 2013). The functional studies showed that specific missense variants create a defective capacity to generate activated protein C (APC), which leads to decreased ability to prevent blood clotting. The TOP Med program conducted extensive whole-genome sequencing analysis, which showed that individuals with VTE possess more rare harmful variants in anticoagulant pathway genes that include PROC (Seyerle A. A, 2023). The study found that people with predicted harmful genetic variants face increased chances of developing VTE. The analysis becomes more difficult because of the different backgrounds found in the population. Vietnamese cohorts demonstrated recurrent and novel PROC mutations enriched in idiopathic DVT cases (Do M. D, 2021), emphasising the need for ancestry-aware variant databases. Collectively, these data position rare PROC variants as emerging high-impact contributors to hypercoagulability in selected idiopathic DVT patients.

F2 VARIANTS BEYOND G20210A

The F2 gene shows its connection with the G20210A polymorphism because this genetic alteration leads to higher prothrombin production, which results in increased thrombin activity. The genetic landscape of this condition

extends beyond this particular genetic mutation. Rare coding mutations may alter prothrombin structure and activity, which leads to enhanced coagulation effects. The G20210A homozygous genotype results in various clinical manifestations, which include both asymptomatic conditions and repeated thrombosis episodes according to (Raymond C. M, 2023). The population exhibits different levels of distribution, which creates significant differences between groups. The prevalence of G20210A in Sri Lankan populations showed a strong decrease when compared to European populations, according to (Gunathilake K. M, 2015). The diagnostic success of G20210A testing shows limitations when used with non-European populations, according to these observed differences. F2-related hypercoagulability includes both classical polymorphisms and rare coding variants, which need detection through sequencing methods.

F9-EVIDENCE GAP AND BIOLOGICAL PLAUSIBILITY

Factor IX participates in the intrinsic pathway amplification of thrombin generation. Elevated factor IX levels have been independently associated with an increased risk of venous thrombosis in population-based studies (Vlieg A. H. V, 2000). However, most F9 mutations that cause haemophilia B are loss-of-function variants. Evidence linking gain-of-function F9 mutations to idiopathic DVT is lacking. Thus, while elevated FIX levels may function as a quantitative risk marker, current evidence does not support routine F9 genetic testing in idiopathic DVT. Although most F9 mutations are classically associated with haemophilia B, experimental and evolutionary analyses of high-specific-activity variants such as factor IX Padua (R338L) demonstrate markedly increased catalytic efficiency and enhanced thrombin generation (Samelson-Jones B. J, 2021). The domain organisation of factor IX and the location of the R338L variant as shown in (Figure 2). These findings establish biological plausibility for a prothrombotic phenotype when FIX activity is substantially elevated. However, population-level evidence linking F9 variants to idiopathic deep vein thrombosis remains limited, and routine F9 genetic screening cannot currently be recommended outside selected or research settings. (Table 1) shows variable strength of association across F2, PROC, and F9, with clear differences in effect size, population distribution, and clinical applicability. PROC variants currently represent the strongest emerging high-risk genetic signal in idiopathic DVT, whereas F2 G20210A remains a well-established but population-dependent contributor. In contrast, F9 variants are biologically plausible but lack robust epidemiologic validation.

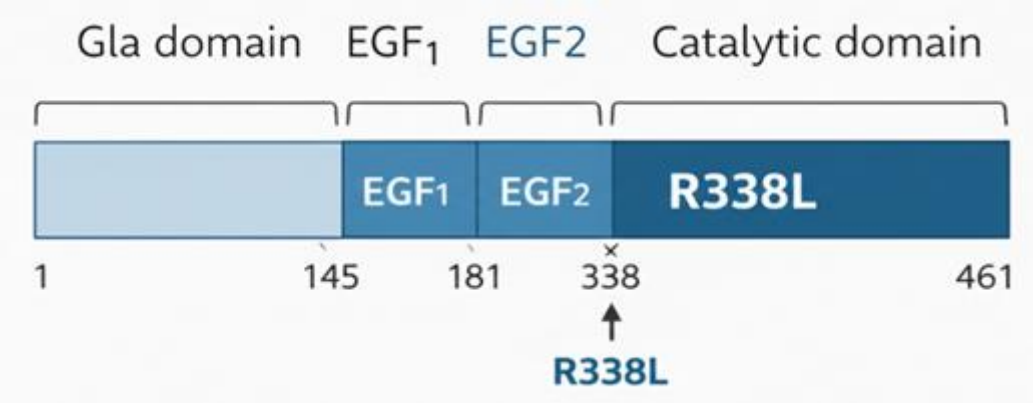

Figure 2. Domain organization of human factor IX (F9) highlighting the R338L gain-of-function variant within the catalytic domain.

Table 1. Genetic Signals in Idiopathic Deep Vein Thrombosis.

Gene	Type of Genetic Signal	Strength of Evidence	Population Pattern	Estimated Risk Impact	Clinical Implication
F2 (Prothrombin)	G20210A (common variant); rare missense variants	Strong for G20210A; limited for rare variants	1-6% in Europeans; <1% in most Asian populations	2-5× (heterozygous); higher in homozygotes	Targeted testing in young, recurrent, or familial unprovoked DVT
PROC (Protein C)	Rare deleterious missense and loss-of-	Strong gene-burden evidence; functional validation	Higher relative contribution in Asian cohorts	7-10× (heterozygous deficiency)	Consider sequencing in early-onset or recurrent idiopathic DVT

	function variants	available			
F9 (Factor IX)	Rare gain-of-function variants (e.g., high-specific-activity mutations)	Mechanistic plausibility; limited epidemiologic evidence	Understudied; rare	Uncertain; case-based data	Not recommended for routine testing; research/selected cases only
Polygenic Risk Score (PRS)	Aggregate common and rare variants	Emerging evidence	Population-dependent	2-3× across highest deciles	Future risk stratification tool; not routine in LMIC settings

RECURRENCE RISK AND IMPLICATIONS OF HIDDEN GENETIC RISK

Recurrence after anticoagulation cessation remains clinically significant, particularly in unprovoked VTE (Linnemann B, 2024). International guidelines recommend that the duration of anticoagulation be individualized based on the balance between recurrence risk and bleeding risk (Ortel T. L, 2020). Severe inherited thrombophilia is recognized as a high-risk condition warranting extended therapy (Linnemann B, 2024). Emerging data on rare PROC variants raise the possibility that genetically confirmed high-impact variants may merit similar consideration. Integrating genetic findings into recurrence-risk models may refine decisions regarding prolonged anticoagulation. Severe inherited thrombophilia, particularly high-impact PROC variants as summarised in (Table 1), may warrant consideration of extended anticoagulation in selected patients.

ANTICOAGULATION IN HIGH-RISK SUBGROUPS

DOACs are now preferred by medical practitioners compared to traditional treatment methods. The study showed that Apixaban decreased VTE cases among high-risk cancer patients while causing only a slight increase in bleeding activities (Carrier M, 2019). The study found that nadroparin lowered thromboembolic events among oncology patients (Agnelli G, 2009), while semuloparin reduced VTE occurrences without causing significant bleeding problems (Agnelli G, 2012).

RESOURCE-LIMITED HOSPITALS USE DIAGNOSTIC PATHWAYS TO CONDUCT MEDICAL EVALUATION

The combination of the Wells criteria with D-dimer testing through structured diagnostic algorithms effectively decreases unnecessary imaging procedures (Hendriksen J. M, 2015). Age-adjusted D-dimer thresholds make it easier to identify older patients who need D-dimer testing (Linnemann B, 2024). Venous duplex ultrasonography remains first-line imaging (Linnemann B, 2024). Genetic testing should be reserved for early-onset, recurrent, familial, or unusual-site thrombosis.

ACCESSIBLE PRECISION PATHWAY PROPOSAL

A pragmatic pathway for tertiary hospitals includes: Clinical triage, Age-adjusted D-dimer, Duplex confirmation, Targeted sequencing of PROC and F2 in selected high-risk patients. Targeted sequencing has demonstrated feasibility in unprovoked VTE cohorts (Wu C, 2013). Precision medicine frameworks support selective genomic integration rather than universal sequencing (Subramanian M, 2020). Cascade testing of relatives may guide prophylaxis during high-risk exposures. As shown in (Table 1), targeted sequencing should prioritize genes with strong evidence and clinically meaningful effect sizes, particularly PROC and F2 in appropriate populations. The proposed tiered precision pathway integrates clinical triage, targeted thrombophilia testing, and selective sequencing in high-risk individuals to optimize management decisions in resource-limited settings. The stepwise clinical-genetic integration model is illustrated in (Figure 3). An integrated conceptual model linking genetic risk spectrum, hypercoagulable mechanisms, idiopathic DVT phenotypes, and a structured precision pathway for resource-limited settings is illustrated in (Figure 4).

BIOMARKERS AND MECHANISTIC INSIGHTS

VTE-associated hypercoagulability arises from the interaction between clinical triggers and intrinsic alterations in the coagulation cascade. The risk of thrombosis increases with elevated levels of coagulation factors, especially factor VIII and factor IX (Pabinger I, 2009). Research experiments demonstrate that circulating tissue factor (TF), which macrovesicles transport, can start and continue the process of thrombosis (Müller I, 2003). New research findings indicate that exosome myeloperoxidase acts as an inflammatory marker, which shows thrombotic activity, thus demonstrating the relationship between inflammation and blood coagulation (Han Y, 2022).

GUIDELINE AND CONSENSUS PERSPECTIVES

International consensus statements establish the evidence-based management approach for VTE treatment, which includes thrombosis prevention techniques. The ACCP 9th edition guidelines established structured recommendations for thromboprophylaxis and duration of anticoagulation, which required doctors to evaluate their patients' specific risk factors before making decisions (Kahn S. R, 2012). The executive summary showed that doctors should evaluate both recurrence and bleeding risks when deciding to use extended treatment (Guyatt G. H, 2012). The 2024 International Consensus Statement recommends prolonged anticoagulation treatment for patients who have ongoing risk factors or severe thrombophilia (Nicolaides A. N, 2024). The American Heart Association has requested that healthcare organizations establish better prevention programs while developing methods to assess risk factors that change over time (Henke P. K, 2020).

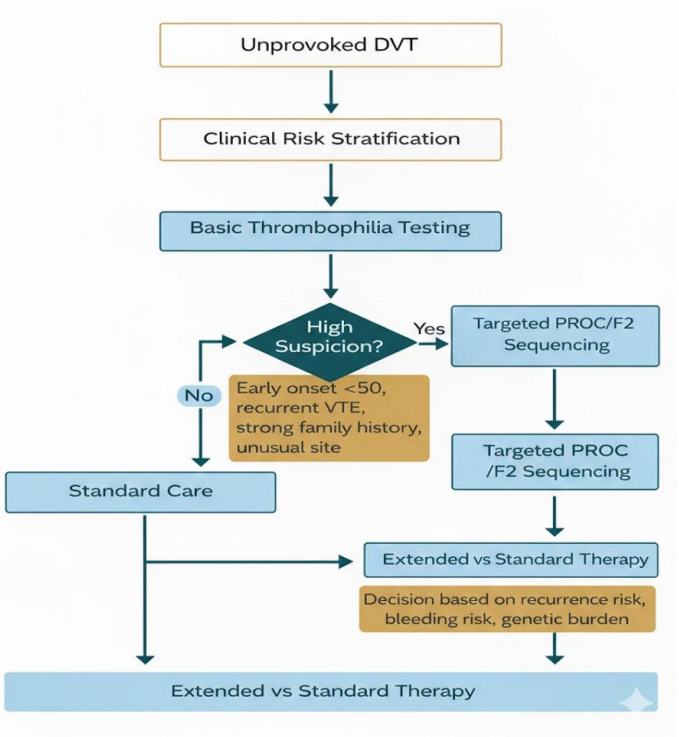

Figure 3. Tiered precision pathway for genetic evaluation in idiopathic DVT.

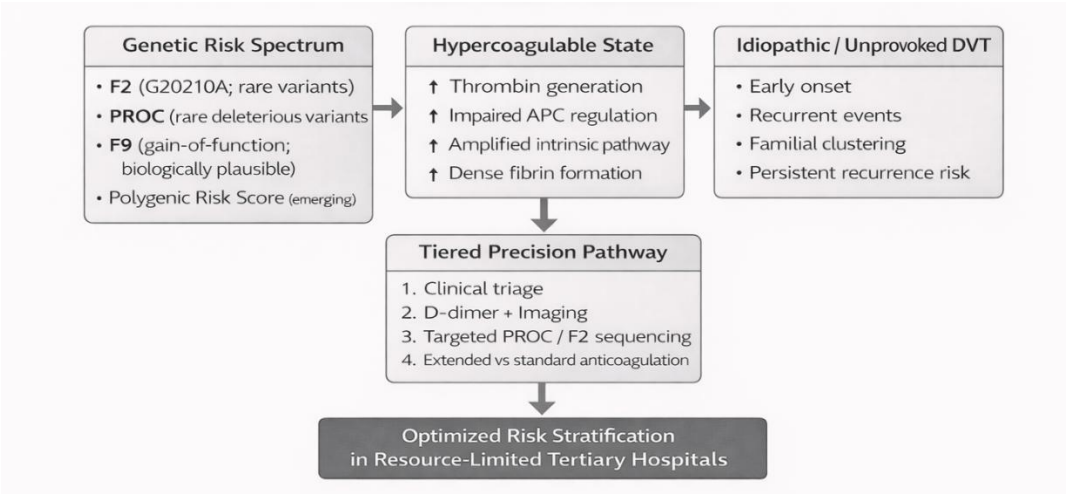

Figure 4. Integrated conceptual model of genetic risk and precision evaluation in idiopathic deep vein thrombosis.

This figure shows how F2, PROC, and F9 variants contribute to hypercoagulability, clinical phenotype, and a tiered precision pathway adapted for resource-limited tertiary hospitals.

CONCLUSION

No implementation trials exist to test structured genetic testing pathways for idiopathic DVT in low- and middle-income countries, despite progress in genomic research. The existing genetic risk data from large sequencing studies do not apply to Asian and other non-European populations because these groups are underrepresented in the research. Population-specific variant databases need development because they serve as critical tools for both accurate interpretation and practical clinical use. Global policy discussions stress the need for improved thrombosis prevention methods and better risk assessment methods to protect different population groups (Lambert J, 2019). Future research should focus on three areas: developing genomic systems that can be expanded, conducting economic assessments of genomic systems, and studying how AI-based triage systems operate in hospitals that lack resources.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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