

Inherited thrombophilia and polygenic risk scores in venous thromboembolism: from classical testing to genomic risk prediction

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ABSTRACT

Venous thromboembolism (VTE) is caused by the interaction between genetic, individually acquired, and environmental factors. The aim of this narrative review is to summarize advances in the research on genetic susceptibility to VTE and its recurrence, focusing on genome-wide association study (GWAS)-derived polygenic risk scores (PRSs) and sequencing-based approaches, and to discuss current barriers to their clinical implementation. Testing for the classical inherited thrombophilias, such as the deficiencies of natural anticoagulants (antithrombin, proteins C and S, the factor V Leiden variant, and the G20210A mutation of factor II) could improve risk stratification and therapeutic decision-making in VTE, although their role in VTE management remains controversial. Over the last 2 decades, knowledge on genetic susceptibility to VTE progressed beyond the classical thrombophilias, thanks to the evolution from single-gene Sanger sequencing to genome-wide sequencing and next-generation sequencing. GWASs have enabled the creation of PRSs combining the effects of multiple single-nucleotide polymorphisms. PRSs could significantly improve VTE risk prediction beyond clinical factors. Integration of genetic and clinical data could improve predictive accuracy. In addition, combining GWAS with transcriptome-wide association studies and Mendelian randomization has shown that genetic risk may change across different clinical presentations of VTE, and that recurrent VTE differs genetically and biologically from the initial event, being associated with genetic variants, such as those of kininogen 1 and fibrinogen. PRSs can stratify VTE risk beyond traditional factors in European-ancestry cohorts; recurrence may have a partially distinct genetic/proteomic architecture. However, prospective clinical utility of these novel approaches to VTE risk stratification remains to be established, and integrating this advanced knowledge into clinical practice remains a future challenge in VTE management.

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Introduction Venous thromboembolism (VTE) encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE). Its estimated annual incidence rates range from 0.75 to 2.69 per

1000 individuals in Western countries,¹ increasing with age and reaching over 5 per 1000 in persons older than 80 years.¹ PE is the third most common cause of cardiovascular death after acute

coronary syndromes and stroke.^{2,3} VTE is caused by the interaction between genetic, individually acquired, and environmental factors. This review outlines classical thrombophilias and current controversies in thrombophilia testing, summarizes recent advances in genome-wide association studies (GWASs) and polygenic risk scores (PRSs), and discusses emerging data on genetics of VTE recurrence and challenges related to their clinical implementation.

Genetics of venous thromboembolism and thrombophilia

The genetic hereditary component of VTE was evaluated in studies involving families, twins, and siblings, and was estimated to range between 35% and 60%.⁴⁻¹¹ However, heritability estimates are inherently heterogeneous and depend on study design, population structure, and statistical modelling approaches. For several years, the rare deficiencies of natural circulating anticoagulants, such as antithrombin (AT), protein C (PC), and protein S (PS), constituted the only known hereditary thrombophilic defects associated with an increased risk of VTE.

The search for genetic hereditary components favoring VTE started in 1965, when AT deficiency was first described by Olav Egeberg in a Scandinavian family with multiple members affected by VTE.¹² Egeberg also demonstrated that the deficiency was an autosomal dominant disorder.¹² For several years, AT deficiency was the only known hereditary defect associated with an increased VTE risk, and was shown to be rare, with prevalence ranging from 0.2–2 per 1000 in the general population.^{13,14} Subsequently, PC was purified from bovine plasma by Johan Stenflo in 1976. The letter C in the name referred to the fact that it was the third protein eluting from the Sepharose column used for the purification.¹⁵ However, the physiological role of PC in the control of blood coagulation was not understood until 1982, when Griffin et al¹⁶ found an association between low plasma PC levels and VTE in a family study. In 1976, Di Scipio et al¹⁷ purified a new vitamin K-dependent plasma glycoprotein. They named it PS, referring to the fact that its isolation and characterization took place in Seattle.¹⁷ However, it was only in 1984 that Schwarz et al¹⁸ described hereditary PS deficiency to be associated with the risk of VTE in a family study.¹⁸ Both PC and PS deficiencies are rare defects, with an estimated prevalence of 3 and 1 per 1000 persons in the general population, respectively.¹⁹

The loss-of-function mutations in the *SERPINC1*, *PROC*, and *PROS1* genes are associated with defects of the natural anticoagulants—AT, PC, and PS, respectively—with several hundreds of mutations described for each gene.²⁰ The nature and functional consequences of the different defects explain the heterogeneity of the clinical phenotype. AT, PC, and PS deficiencies are very rare, as the risk of VTE has mainly been evaluated in family studies, while among unselected consecutive patients with VTE, the risk associated with

these defects is estimated to be lower than in selected thrombophilic families.^{19,20} As a result, familial thrombophilia per se could be the cause of additional, yet unknown, defects.^{21,22}

Thrombophilic defects evolved from being considered rare mutations of natural anticoagulants with loss of function to being viewed as common gain-of-function polymorphisms in 1993, when Dahlbäck et al²³ described the resistance to activated PC (APC resistance)²³ as a common and strong risk factor for VTE.²⁴ Subsequently, in 1994, Bertina et al²⁵ from Leiden showed that, in a majority of cases, inherited APC resistance was caused by a single mutation (factor [F] V Leiden [FVL], rs6025) in the FV gene.^{25,26} The Arg506 to Gln mutation is situated in the part of the gene encoding for 1 of the 3 cleavage sites in FV (Arg306, Arg506, and Arg679) where PC inactivates FVa. Consequently, FVL is resistant to the inactivation by PC, which results in a gain, rather than a loss, of function.²⁶⁻²⁹ The risk of thrombosis increases 5-fold in heterozygotes and 50-fold in homozygotes.²⁶⁻²⁹ The description of APC resistance and the role of FVL transformed hereditary thrombophilia into a common disorder. In fact, FVL has a prevalence of 5%–10% in the general white population, and it is found in 20%–30% of individuals with VTE and approximately 50% of patients in thrombophilic families.²⁶⁻²⁹ Other, more rare variants of FV that carry resistance to PC have also been described.²⁹ In 1996, another gain-of-function polymorphism was reported by Poort et al,³⁰ namely a G-to-A transition at nucleotide 20210 (prothrombin G20210A, rs1799963) in the 3'-untranslated part of the prothrombin (FII) gene. This polymorphism is associated with elevated prothrombin levels and an increased risk of VTE.³⁰ The G20210A prothrombin polymorphism is also common, with a prevalence of 2%–5% in the general population, and it is found almost exclusively in white patients. Heterozygotes have a 2- to 3-fold increased risk of VTE, and the variant can be detected in approximately 6% of patients with VTE.^{30,31} Homozygosity for the G20210A prothrombin mutation variant is rarer than homozygosity for the FVL variant. The risk of VTE has been reported to be 30-fold higher for homozygotes of the G20210A prothrombin mutation as compared with the general population.^{31,32}

Thrombophilia testing The mutations causing inherited deficiencies of AT, PC, and PS can be assessed routinely in specialized coagulation laboratories. Their decreased plasma levels in immunological assays indicate quantitative defects or type I deficiency, while functionally abnormal protein molecules are associated with qualitative defects or type II deficiency.³¹ However, the genetic evaluation of the defects of natural anticoagulants is usually not routinely performed, except for specialized research laboratories. In contrast, the detection of single-nucleotide

TABLE 1 Classical inherited thrombophilias: prevalence, relative risk of first venous thromboembolism, and diagnostic modalities

Variant/deficiency	Prevalence in the general population	Relative risk of first VTE	Testing modality	Key clinical considerations
Antithrombin deficiency	0.02%–0.2% ^{11,12}	10–20-fold ^{17,18}	Functional assay ± <i>SERPINC1</i> sequencing	High-risk, rare; strong family aggregation
Protein C deficiency	Approx. 0.2%–0.4% ¹⁷	5–10-fold ^{17,18}	Functional + antigenic assay ± <i>PROC</i> sequencing	Variable penetrance; acquired reductions common
Protein S deficiency	Approx. 0.03%–0.13% ¹⁷	5–10-fold ^{17,18}	Free protein S antigen ± <i>PROS1</i> sequencing	Influenced by pregnancy, OCPs, inflammation
Factor V Leiden (heterozygous)	5%–10% (white population) ^{23–26}	3–7-fold ^{23–26}	APC resistance assay + PCR	Most common inherited risk factor
Factor V Leiden (homozygous)	<0.1% ^{23–26}	50-fold ^{23–26}	PCR	High thrombotic risk, especially with additional factors
Prothrombin G20210A (heterozygous)	2%–5% ^{28–31}	2–3-fold ^{28–31}	PCR	Moderate thrombotic risk; often combined with factor V Leiden
Prothrombin G20210A (homozygous)	Rare (<0.01%) ³¹	Up to 30-fold ³¹	PCR	Rare; risk data based on limited cohorts

Abbreviations: APC, activated protein C; OCP, oral contraceptive pill; PCR, polymerase chain reaction; VTE, venous thromboembolism

mutations of FVL and the G20210A mutation of prothrombin have become largely available also in nonspecialized coagulation laboratories.³³ FVL can also be detected with a laboratory phenotype test of APC resistance and can be confirmed with a genetic analysis; in some cases, only the genotype is determined with molecular analysis, without the phenotypic APC resistance test.³⁴ In contrast to FVL, the G20210A prothrombin mutation can only be detected with genetic analysis. FV variants other than FVL can determine APC resistance but they are not tested routinely, even in the cases that are positive for APC resistance but negative for FVL.³³ Other genetic causes of thrombophilia, such as AT resistance, FVIII, and FIX Padua, have been recently described in families but not in large cohorts, and it is still unknown how frequent they are among patients with thrombosis.³¹ In addition, high plasma levels of clotting factors, such as FVIII, FIX, FX, FXI, von Willebrand factor (vWF), and fibrinogen can be considered in a thrombophilia panel; however, data from large cohorts are limited, and the genetic basis of increased levels of these factors is only partially known.³⁵

In current clinical practice, the panel routinely employed for thrombophilia screening encompasses testing for the defects of natural anticoagulants (AT, PC, and PS) as well as the FVL and G20210A prothrombin mutations. These are defined as classical thrombophilias.³¹ However, their clinical utility has been debated for many years. Thrombophilia testing does not fully encompass the complexity of VTE pathophysiology, and its role in guiding the management of VTE remains controversial.³⁴ Data on clinical usefulness and benefits of testing for primary and secondary prevention of VTE based on thrombophilia status alone are extremely limited.^{34,36} Guidelines of the American Society of Hematology (ASH) on thrombophilia screening³⁶ do not

recommend universal testing; they advise that testing be performed only in the cases when a positive result would change patient management, albeit with low-certainty evidence due to the lack of high-quality outcome data. However, a survey of 82 laboratories adhering to the International Society on Thrombosis and Haemostasis external quality control schemes on thrombophilia testing³³ has shown that classical thrombophilia testing is in fact commonly performed. Laboratories perform plasma-based thrombophilia testing, but 42% declare doing so only in the case of requests from thrombosis/hemostasis specialists, in patients without anticoagulant treatment, or those with a strong personal or familial history of VTE. In addition, testing is not always performed according to published guidelines, often with inadequate adoption of reference intervals from manufacturers or from the literature. Genetic testing is mostly restricted to single-variant testing.³³

The principal types of inherited classical thrombophilia, including their prevalence, relative risk estimates, and diagnostic modalities, are summarized in [TABLE 1](#).

Thrombophilic defects can be stratified according to their associated risk of VTE into high-, moderate-, and low-risk categories. High-risk thrombophilias include the defects of natural anticoagulants, such as AT deficiency and homozygous PC or PS deficiency, which are typically associated with the greatest thrombotic burden, as well as acquired thrombophilia, such as antiphospholipid antibody syndrome. Moderate-risk thrombophilias include combined hereditary defects, homozygous FVL or prothrombin G20210A mutation, and heterozygous PC or PS deficiency. In contrast, isolated heterozygous FVL or prothrombin G20210A mutations are generally considered low-risk thrombophilias. This pragmatic classification might help guide the intensity of counselling, prophylaxis in high-risk situations,

TABLE 2 Classification of thrombophilia according to the risk of venous thromboembolism

High-risk thrombophilia	Moderate-risk thrombophilia	Low-risk thrombophilia
Antithrombin deficiency	Combined hereditary thrombophilia ^a	Factor V Leiden (heterozygous)
Homozygous Factor V Leiden or prothrombin (factor II) G20210A	Protein C deficiency (heterozygous)	Prothrombin (factor II) G20210A (heterozygous)
Protein C deficiency (homozygous)	Protein S deficiency (heterozygous)	
Protein S deficiency (homozygous)		

^a Refers to the coexistence of ≥2 inherited thrombophilic defects, such as Factor V Leiden plus prothrombin (factor II) G20210A, or a high-risk defect (eg, antithrombin, protein C, or protein S deficiency) combined with another inherited thrombophilic abnormality

and decisions around continued anticoagulation in selected patients (TABLE 2).

A summary of the most recent recommendations on the use of thrombophilia testing published by the ASH³⁶ and their comparison with the International Consensus Statement (ICS)³⁷ is provided in TABLES 3–6. These 2 documents differ with respect to their methodological design. The ASH guidelines were developed by a multidisciplinary panel, with the adoption of the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach,³⁶ whereas the ICS is not strictly a guideline, but a consensus. As the quality of evidence in this area is low, most of the ASH recommendation are conditional.

When does thrombophilia testing change patient management? The clinical utility of thrombophilia testing depends on whether the result is expected to alter patient management. Contemporary guidelines discourage routine testing in unselected patients with VTE, particularly when it does not influence decisions regarding anticoagulation duration or family counselling.^{34,36}

According to the 2023 ASH guidelines,³⁶ thrombophilia testing may be considered in selected clinical scenarios in which the result is likely to modify management, including: 1) patients who experienced VTE at a young age and have a strong family history of thrombosis, particularly when high-risk deficiencies (AT, PC, or PS) are suspected; 2) women with a history of VTE who are considering pregnancy or estrogen-containing contraception. In women with a family history of VTE and thrombophilia who are planning pregnancy, selective testing for the thrombophilia type known in the family is suggested to decide on ante- and postpartum thromboprophylaxis. Women with known homozygous FVL, a combination of FVL and prothrombin gene mutation, or AT deficiency should receive ante- and postpartum thromboprophylaxis. In the case of known PC or PS deficiency in the family, testing is left to the physician’s discretion to guide antepartum thromboprophylaxis. However, in the case of a positive result for PC or PS deficiency, postpartum thromboprophylaxis is suggested. In addition, in the case of a known combination of FVL and prothrombin gene mutation or AT deficiency in second-degree relatives, testing for the thrombophilia type present in the family is suggested, along with postpartum thromboprophylaxis in

the women with thrombophilia. With respect to women considering estrogen-containing contraceptives or hormone replacement therapy, there is a strong recommendation to avoid routine screening, except for the women whose family members have a known PC, PS, or AT deficiency, and to avoid estrogen containing-contraceptives or hormone replacement therapy in those with thrombophilia; 3) individuals with VTE in atypical sites (eg, splanchnic or cerebral veins); and 4) selected cases in which identification of a high-risk thrombophilia may influence the decision regarding extended anticoagulation.³⁵

In contrast, routine thrombophilia testing is generally not recommended after a first provoked VTE episode, in elderly patients without a suggestive family history, or when the result would not affect the therapeutic strategy.³⁶ Importantly, the presence of common variants, such as FVL or prothrombin G20210A mutation, rarely changes the duration of anticoagulation after a first VTE event.^{34,36} Furthermore, testing should be avoided during the acute thrombotic phase or during anticoagulant therapy, as this may lead to inaccurate results, particularly for functional assays of AT, PC, and PS.^{34,36} The overall quality of evidence supporting many testing recommendations remains low to moderate, largely due to the absence of randomized outcome trials evaluating management strategies guided by thrombophilia status.^{34,36} Therefore, testing decisions should be individualized and integrated with clinical risk assessment.

Genome-wide association studies Beyond the classical thrombophilias, advances in molecular genetics over the past decade have shifted the focus from single-gene defects (single-gene Sanger sequencing) to genome-wide exploration of common genetic variations. Genome-wide association studies (GWASs) have enabled systematic exploration of the polygenic architecture of VTE.³⁸ GWAS is a genome-wide analysis of genotypes that can be measured using different technologies, for example, whole-genome sequencing or genome-wide single-nucleotide polymorphism (SNP) arrays plus imputation. However, most GWASs are still performed using data from SNP arrays.³⁸ GWASs involve testing of thousands up to millions of genetic variants across the genomes of many subjects to identify genotype–phenotype associations. Therefore, they require the availability and

access to biobanks storing large numbers of DNA samples with related clinical data, such as the Million Veteran Program (MVP), the United Kingdom Biobank (UKB), or FinnGen. Such biobanks have allowed researchers to link millions of genetic variants to thousands of human phenotypes (or traits), as well as molecular phenotypes, such as transcriptomics and proteomics.^{39,40}

GWASs have substantially changed the field of complex disease genetics over the past decades.^{41–45} Since 2005, when the first GWAS on age-related macular degeneration was described, more than 50 000 associations of genome-wide significance have been reported between genetic variants and common diseases and traits.⁴³ These associations have allowed insights into disease susceptibility for many conditions, including VTE.^{44,45} Several new VTE disease loci have been described, and previously discovered VTE loci have been confirmed by GWASs.⁴⁶

However, it was subsequently realized that GWAS-confirmed loci typically have small effect sizes, with relative risks between 1 and 1.5, and can be associated with only a modest proportion of trait heritability.³⁸ In addition, GWASs are limited by an important burden of multiple testing, with of a high level of significance to account for the multiple tests (eg, increasing the sample size), and thus the cost of testing. GWASs can explain only a modest fraction of the missing heritability, probably due to the stringent threshold of significance. Beyond the restrictive statistical thresholds, several additional factors contribute to the phenomenon of “missing heritability.” These include the limited detection of rare variants and structural genomic alterations, incomplete capture of gene–gene and gene–environment interactions, phenotypic heterogeneity, and residual population stratification. Furthermore, classical twin-based heritability estimates may reflect both additive and nonadditive genetic effects, which are not fully captured by common-variant GWAS models.^{47,48} Another limitation of GWASs is that rare variants, such as those causing deficiencies of AT, PC, and PS, will not be detected, even in very large studies.^{47,48} In contrast, GWASs predominantly detect common variants with small effect sizes, which explain only a limited proportion of the total phenotypic variance.³⁸ As a result, the clinical predictive value of GWASs per se is quite limited. In addition, the common variants detected in these studies may be related to the genes of components that are not clearly related to the hemostatic system and whose pathophysiological role in VTE may be obscure. However, the identification of a large number of variants, although weak, allows for the creation of genetic or polygenic risk scores (PRSs).^{49,50} PRSs are quantitative measures of risk summed across multiple risk alleles. For some diseases, PRSs have shown the ability to divide a population into sufficiently distinct risk categories to influence clinical and personal decision-making.

Polygenic risk scores in venous thromboembolism Recently, Ghouse et al⁴⁹ performed a GWAS meta-analysis of 6 cohorts comprising 81 190 cases and 1 419 671 controls of European descent to detect new risk loci for VTE and to develop a PRS for VTE. The 6 studies included samples from biobanks, such as the Copenhagen Hospital Biobank Cardiovascular Disease Cohort, the Danish Blood Donor Study, deCODE, Intermountain Healthcare, UKB, FinnGen, and MVP, comprising approximately 9.6 million sequence variants.⁴⁹ A total of 93 loci met conventional genome-wide level of significance ($P < 5 \times 10^{-8}$), of which 62 were novel, that is, not overlapping with a previously reported locus for VTE.

The authors also investigated whether PRSs could identify at-risk individuals and increase or mitigate the risk associated with known thrombophilia genes (ie, FVL and prothrombin mutations) and traditional risk factors.⁴⁹ The PRS for VTE was derived using polygenic prediction via Bayesian regression and continuous shrinkage priors (PRS-CS) and a derivation sample (without the UKB) including 57 467 cases and 1 006 954 controls.⁴⁹ The obtained risk score could effectively identify both high- and low-risk individuals. Those within the top 0.1% of PRS distribution had a VTE risk similar to homozygous or compound heterozygous carriers of the variants G20210A in FII and FVL. The authors also found that the FII and FV mutation carriers in the bottom 10% of the PRS distribution had a VTE risk similar to that of the general population.⁴⁹ If these results are confirmed, current recommendations regarding the testing for classical thrombophilias (TABLES 1–3) should be regarded with caution. PRSs could improve individual risk prediction beyond that based on genetic and clinical risk factors. The authors calculated the 10-year risk of VTE according to the PRS and clinical (sex, age, smoking status) risk factors. In addition to relative risk estimates, they reported the area under the receiver operating characteristic curve (AUC) and demonstrated risk stratification across PRS percentiles, showing incremental predictive value beyond traditional clinical risk factors.⁴⁹ Calibration analyses and absolute 10-year risk estimates were also provided, enhancing clinical interpretability.

Transparent reporting of PRSs is essential for clinical translation. Contemporary reporting standards recommend that PRS studies clearly specify ancestry and population characteristics, variant selection and weighting methodology, discrimination metrics (AUC or C-index), calibration performance, absolute risk stratification, and assessment of clinical utility.⁵¹

More recently, Munsch et al⁵² conducted a GWAS meta-analysis of data from 6355 individuals with a first VTE—1775 of whom experienced VTE recurrence—across 8 prospective cohorts of European ancestry to assess genetic factors associated with recurrent VTE.⁵² The authors also employed transcriptome-wide association

TABLE 3 Recommended thrombophilia testing according to the clinical context (provoked and unprovoked event) and targeted workup as published by the American Society of Hematology guidelines on thrombophilia testing³⁶ vs the International Consensus Statement³⁷

Clinical scenario	Who to test		What to test (suggested panel)		Evidence/strength (if stated)		Rationale/impact on management	
	ICS	ASH	ICS	ASH	ICS	ASH	ICS	ASH
Unprovoked VTE (index event)	First episode of unprovoked VTE <50 y, with or without family history	Do not test	Inherited thrombophilia panel ^a ± aPL testing	No tests	–	Low/conditional	May help in recurrence risk assessment, family counselling, and selected management decisions	Testing does not influence decisions on duration of anticoagulation as the guidelines recommend long-term anticoagulation regardless of thrombophilia
	Unprovoked VTE (any age)	Do not test	aPL testing (lupus anticoagulant, anticardiolipin, anti-β2GPI)	No tests	Low/strong	Low/conditional	May alter long-term management and the choice of an anticoagulant (eg, APS considerations)	
Provoked VTE	VTE provoked by a nonsurgical major transient risk factor	Test for thrombophilia	Inherited thrombophilia panel ^a (selective)	Thrombophilia panel	–	Low/conditional	May support risk stratification when the provoking factor is not surgical/major operative	Indefinite anticoagulant treatment for patients with thrombophilia
	VTE provoked by a minor risk factor	–	aPL testing	–	Low/weak	–	May alter antithrombotic choice/duration if APS identified	–
	VTE provoked by surgery	–	No tests	No tests	–	Low/conditional	–	Stop anticoagulation after completion of the primary treatment

a Recommended inherited thrombophilia panel: antithrombin, protein C, protein S (functional assays), factor V Leiden, prothrombin G20210A mutation (± additional variants per local practice). Testing should be timed appropriately (avoid acute thrombosis phase and anticoagulant interference when possible).

Abbreviations: aPL, antiphospholipid antibody; APS, antiphospholipid syndrome; ICS, International Consensus Statement; others, see [TABLE 1](#)

studies and Mendelian randomization (MR), in which genetic variants corresponding to modifiable exposures (eg, biochemical markers or physiological traits) are analyzed with respect to clinical outcomes. MR can test whether such exposures causally influence disease risk. Using these approaches, 28 molecular markers associated with VTE recurrence were identified, including 1 novel gene locus (*GPR149*). Among all variants known to be associated with the first VTE, kininogen 1 (*KNG1*), and fibrinogen (*FGG*) were associated with recurrence. Additionally, MR analyses identified 7 proteins as risk factors for recurrence: elevated plasma levels of FXI, FVIII, vWF, histo-blood group ABO system transferase (BGAT), and Golgi membrane protein 2; and decreased levels of proprotein convertase subtilisin/kexin type 9 and pro-interleukin-16. Subgroup analyses identified 18 molecular determinants associated with VTE recurrence, with notable differences between the subgroups.⁵³ The findings of this study challenge the understanding of VTE and its recurrence in fundamental ways.⁵³

Among previously established genetic and biochemical markers associated with the first VTE, only 2 genetic markers (*KNG1* and *FGG*) and 4 genetically-determined protein levels (FXI, BGAT, vWF, and FVIII) were found to be linked to VTE recurrence.^{52,53} This implies that the risk of recurrent VTE is genetically and biologically distinct from the initial VTE risk, revolutionizing the existing paradigms of VTE. These findings support a partially distinct molecular architecture of VTE recurrence; however, the incremental clinical benefit and impact on decision-making require prospective validation before their routine implementation. The study also explored how genetic risk may diverge across different clinical presentations of VTE.⁵³ In subgroup analyses, 18 molecular markers were identified as being associated with VTE recurrence only in specific clinical contexts, such as sex, provoked or unprovoked VTE status, or the type of initial VTE. For instance, the exonic *SLC4A1* variant p.Glu40Lys was associated with a 3-fold increased risk of recurrence in patients with PE but not in those with DVT—which reinforces the emerging notion that PE and DVT differ at the molecular level.⁵³ These findings challenge the conventional concept that thrombophilia testing is of limited utility while genetics—when scaled appropriately and interpreted through updated robust analytic frameworks—can explain pathways that could guide secondary VTE prevention. As the tools of genomic medicine become more accessible, more research is required to incorporate these findings into clinical practice to personalize anticoagulation decisions in patients with VTE.

The ABO locus is a well-established genetic determinant of VTE. A haplotype-based association study from China, using ABO-tagging SNPs (including rs512770, which distinguishes between O1.1 and O1.2) in 1576 VTE cases and 17 535 ancestry-matched controls, evaluated

TABLE 4 Recommended thrombophilia testing according to the clinical context (women-specific triggers) and targeted workup as published by the American Society of Hematology guidelines on thrombophilia testing³⁶ vs the International Consensus Statement³⁷

Who to test		What to test (suggested panel)		Evidence/strength (if stated)		Rationale/impact on management	
ICS	ASH	ICS	ASH	ICS	ASH	ICS	ASH
–	Provoked by pregnancy or postpartum	Inherited thrombophilia panel ^a (selective) ± aPL	Test for thrombophilia	–	Low/conditional	May influence counselling and prophylaxis in future pregnancies	Indefinite anticoagulant treatment for patients with thrombophilia
–	Associated with the use of COCs	Inherited thrombophilia panel ^a (selective)	Test for thrombophilia	–	Low/conditional	May affect contraceptive choices and future prophylaxis decisions	Indefinite anticoagulant treatment for patients with thrombophilia
–	–	Antithrombin activity (timing per anticoagulant exposure)	–	Low/weak	–	High-risk thrombophilia; may change prophylaxis intensity and explain heparin resistance	–
History of unprovoked VTE: repeat testing	–	Repeat aPL testing outside pregnancy	–	Low/weak	–	Pregnancy can affect assays; confirmation guides long-term management	–

a Recommended inherited thrombophilia panel: antithrombin, protein C, protein S (functional assays), Factor V Leiden, prothrombin G20210A (± additional variants per local practice). Testing should be timed appropriately (avoid acute thrombosis phase and anticoagulant interference when possible).

Abbreviations: COCs, combined oral contraceptives; others, see TABLES 1 and 3

the effects of ABO haplotypes on VTE risk and recurrence.⁵⁴ In individuals from East Asia, the rs1053878-A allele is consistently coinherited with the rs2519093-T allele, precluding its use as a specific marker for the A2 blood group, unlike in Europeans.⁵⁴ All non-O1 haplotypes were homogeneously associated with an approximately 1.4-fold increased risk of VTE ($P = 5.2 \times 10^{-20}$) and an approximately 1.7-fold increased risk of recurrence ($P = 0.023$), as compared with the O1.1 group.⁵⁴

In a Thai case-control genotyping study (122 VTE cases; 87 matched controls), 7 SNPs showed significant associations with VTE, including 5 risk alleles (*PROC*, *ABO*, *FGG*, *FXI*, *HIVEP1*) and 2 protective alleles (*FV*, *TGFB2*).⁵⁵ A combined PRS integrating genetic and clinical factors predicted recurrence, particularly in unprovoked VTE, with an over 3-fold higher recurrence risk. These findings provide population-specific evidence for genetic susceptibility to VTE in Thais, and support PRS-informed recurrence stratification using a scalable, cost-effective MassARRAY SNP panel.⁵⁵

Current clinical models—such as HERDOO2 (Hyperpigmentation, Edema, or Redness in either leg; D-dimer level ≥ 250 $\mu\text{g/L}$; Obesity with body mass index ≥ 30 ; or Older age, ≥ 65 years), DASH (D-dimer, Age, Sex, Hormonal therapy), or Vienna prediction scores—rely exclusively on clinical and laboratory variables and provide limited predictive accuracy.⁵⁰ Consequently, a large proportion of patients are either exposed to an unnecessary bleeding risk due to prolonged anticoagulation or experience recurrent

thrombosis after discontinuation. The findings by Munch et al⁵³ demonstrated that the genomic architecture of VTE recurrence is distinct from that of the first event, identifying multiple loci and proteins (eg, *GPRI49/MME*, *KNG1*, *FGG*, *FXI*, *FVIII*, and *vWF*) associated with recurrence and highlighting the value of PRSs to stratify recurrence risk. Integrating these genetic determinants with clinical features and functional biomarkers (eg, thrombin generation, D-dimer, FVIII) could provide a robust individualized estimate of recurrence risk and support personalized discontinuation of anticoagulant therapy.

Next-generation sequencing Another evolution of genetics is the development and availability of several so-called next-generation sequencing (NGS) or high-throughput nucleotide sequencing platforms. NGS allows for the generation of fast, inexpensive, and accurate genomic information, as reviewed by Cunha et al.⁵⁶ NGS studies can either employ whole-exome sequencing or whole-genome sequencing; they can also be used for re-sequencing of targeted candidate gene.^{57,58} NGS enables the detection of rare single-nucleotide variants, structural rearrangements, copy number variants, and mutations in regulatory or noncoding regions.⁵⁶ This technology is especially useful in revealing oligogenic or polygenic contributions to thrombosis, which often go undetected in standard workups. A major problem is that the studied mutations are often rare; therefore, even if mutation gene enrichment is employed, large studies would be necessary. The use of NGS may be more justified in selected high-yield clinical scenarios,

TABLE 5 Recommended thrombophilia testing according to the clinical context (different VTE conditions) and targeted workup as published by the American Society of Hematology guidelines on thrombophilia testing³⁶ vs the International Consensus Statement³⁷

Clinical scenario	Who to test		What to test (suggested panel)		Evidence/strength (if stated)		Rationale/impact on management	
	ICS	ASH	ICS	ASH	ICS	ASH	ICS	ASH
Recurrent thrombosis	Considered	Not considered						
			Inherited thrombophilia panel ^a ± aPL	–	Low/weak	–	Supports phenotyping; may influence counselling and selected treatment decisions; suggests systemic prothrombotic tendency rather than local venous disease	–
Unusual-site thrombosis	Symptomatic VTE at unusual sites (eg, cerebral venous thrombosis, splanchnic thrombosis without cirrhosis)	Cerebral venous thrombosis, splanchnic thrombosis	aPL; consider MPN panel/JAK2; consider PNH in the case of blood cell count abnormalities	In the settings where anticoagulation would otherwise be discontinued after primary short-term treatment; test in the settings where anticoagulation would otherwise be continued indefinitely; do not test	Low/weak	Low/conditional	Unusual-site thrombosis raises suspicion of APS/MPN/PNH; results can change anticoagulant choice and prompt disease-specific therapy	Indefinite anticoagulant treatment for patients with thrombophilia
			JAK2 mutation testing	–	Low/weak	–	Occult MPN can present with SVT/CVST even with normal blood cell counts	–
Catastrophic/fulminant presentations	Acute multiple thrombotic events with organ failure suggestive of CAPS	Not considered	aPL testing	–	Low/strong	–	Diagnosis drives urgent, specific treatment strategies	–
			Protein C, protein S, antithrombin (focus on severe deficiencies)	–	–	–	Identifies severe inherited deficiency with major therapeutic implications	–

a Recommended inherited thrombophilia panel: antithrombin, protein C, protein S (functional assays), Factor V Leiden, prothrombin G20210A (± additional variants per local practice). Testing should be timed appropriately (avoid acute thrombosis phase and anticoagulant interference when possible).

Abbreviations: CAPS, catastrophic antiphospholipid syndrome; CVST, cerebral sinus vein thrombosis; JAK2, Janus kinase 2; MPN, myeloproliferative neoplasm; PNH, paroxysmal nocturnal hemoglobinuria; VST, splanchnic vein thrombosis; others, see TABLES 1 and 3

such as patients with early-onset thrombosis, strong familial clustering, severe deficiency of natural anticoagulants with inconclusive standard test results, suspected monogenic thrombophilia, or recurrent episodes of idiopathic VTE. In these contexts, targeted gene panels may increase diagnostic yield, although the probability of identifying pathogenic variants depends strongly on the clinical phenotype and pretest probability.^{59,60}

Current evidence supporting the use of PRS genomic approaches in VTE is subject to several important limitations. Most large-scale GWAS and PRS derivation cohorts have included predominantly individuals of European ancestry, limiting generalizability across populations.^{49,60} Evidence of clinical utility remains indirect, as randomized or decision-impact studies evaluating PRS-guided management strategies are lacking.⁶¹ There is currently no standardized framework for implementation in routine practice, and issues related to cost-effectiveness, laboratory infrastructure, and ethical considerations—including incidental findings and genetic counselling—remain unresolved.^{51,61}

Future research should prioritize prospective validation of integrated risk models that combine PRSs with established clinical predictors and functional biomarkers, such as D-dimer, FVIII, and thrombin generation parameters, to determine their incremental predictive value and clinical utility.^{49,52} Cross-ancestry validation and recalibration of PRSs are essential to enhance generalizability across populations.^{49,61} In addition, decision-impact studies are needed to evaluate whether PRS-informed strategies meaningfully influence the duration of anticoagulant therapy and improve patient-centered outcomes after the first VTE episode.^{36,49} Future investigations should also assess net clinical benefit and cost-effectiveness of genomic risk stratification within real-world health care systems. Finally, development of standardized implementation frameworks and adherence to established reporting standards for PRSs are necessary before genomic testing can be responsibly integrated into thrombophilia assessment.⁵¹ Integration of genomic risk models with existing clinical guidelines requires alignment with contemporary national recommendations and further validation within diverse health care systems.^{62–64}

Experience from the real-life implementation of international thrombosis guidelines in other clinical settings, such as cancer-associated thrombosis, illustrates the gap that may exist between formal recommendations and routine practice, highlighting the need for structured implementation strategies before introducing novel genomic risk tools.^{63,64}

Conclusions GWASs have substantially expanded our understanding of the polygenic architecture of VTE beyond the classical inherited thrombophilias. The cumulative contribution of multiple common variants has enabled the development

TABLE 6 Recommended thrombophilia testing according to the clinical context (family-based testing and cancer setting) and targeted workup as published by the American Society of Hematology guidelines on thrombophilia testing⁴⁵ vs the International Consensus Statement³⁷

Clinical scenario	Who to test		What to test (suggested panel)		Evidence/strength (if stated)		Rationale/impact on management	
	ICS	ASH	ICS	ASH	ICS	ASH	ICS	ASH
Family-based testing	Asymptomatic relatives of individuals with known thrombophilia (first-/second-degree; multiple relatives; young index case)	Asymptomatic individuals with a family history of VTE and known thrombophilia presenting with a minor transient provoking risk factor (eg, immobility or minor injury, illness or infection)	Targeted inherited thrombophilia testing guided by the family defect ^a	ASH	–	Low/conditional	Informs counselling, avoidance of high-risk exposures, and prophylaxis in high-risk situations	Use thromboprophylaxis in individuals with thrombophilia
				• Strategy 1: selective testing for the thrombophilia known in the family; no testing in the case of heterozygous FVL or heterozygous PGM • Strategy 2: inherited thrombophilia panel, but not in the case of heterozygous FV or heterozygous PGM • Protein C, S, or antithrombin deficiency: test for all hereditary thrombophilias				
Cancer setting	Asymptomatic first-degree relatives of probands with protein C, protein S, or antithrombin deficiency, when results would change patient management	Asymptomatic individuals with a family history of thrombophilia but no personal history of VTE	Targeted testing for the known deficiency	ASH	Low/weak	Low/conditional	Selective testing indicated only when it will meaningfully influence decisions (eg, pregnancy, hormone-based therapies, surgery)	Use thromboprophylaxis in individuals with thrombophilia
				• Heterozygous FV or heterozygous PGM: no testing • Protein C, S, or antithrombin deficiency in first-degree relatives: test for the thrombophilia type known in the family; if in a second-degree relative: do not test				
Cancer setting	Ambulatory/hospitalized cancer patients at a low-to-moderate VTE risk but with a family history of VTE in first-degree relatives	Ambulatory patients with cancer classified to be at low or intermediate VTE risk, who have a family history of VTE in first-degree relatives	Selective inherited thrombophilia testing ^a	ASH	–	Low/conditional	May refine prevention strategy in borderline-risk patients	Use thromboprophylaxis in individuals with thrombophilia
				Doing a thrombophilia panel test for all hereditary thrombophilias (panel)				

a Recommended inherited thrombophilia panel: antithrombin, protein C, protein S (functional assays), Factor V Leiden, prothrombin G20210A ($\pm$ additional variants per local practice). Testing should be timed appropriately (avoid acute thrombosis phase and anticoagulant interference when possible)

Abbreviations: F, factor; FVL, factor V Leiden; PGM, prothrombin G20210A mutation; others, see TABLES 1 and 3

of PRSs, which may complement traditional clinical risk assessment, particularly in individuals of European ancestry. Emerging data also suggest that the molecular determinants of recurrent VTE may differ, at least partially, from those of the first event, challenging conventional paradigms of thrombosis risk stratification. The evaluation of these molecular determinants could help define the duration of anticoagulant treatment in patients with the first episode of VTE. However, PRSs do not account for gene–environment interactions and lifestyle characteristics.³⁵ A strong family history of VTE, without any classical inherited thrombophilias, in a patient who develops VTE is per se an indicator of a high VTE risk. Yet, the integration of PRSs with clinical data could better identify the individuals at a higher risk of recurrence, and thus determine the optimal duration of anticoagulant treatment.

Despite promising advances, the translation of genomic findings into routine clinical practice requires further prospective validation, standardized implementation strategies, and proof of clinical utility and cost-effectiveness. At present, genomic tools should be viewed as complementary to—rather than replacements for—established clinical assessment in the management of VTE.

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