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Article type: Review article

Received: March 12, 2026.

Revision accepted: April 23, 2026.

Published online: May 4, 2026.

ISSN: 1897-9483

Pol Arch Intern Med.

doi:10.20452/pamw.17287

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 a disorder due to the interaction between genetic, individually acquired and environmental factors. The aim of this narrative review is to summarize advances in genetic susceptibility to first and recurrent VTE, focusing on GWAS-derived polygenic risk scores and sequencing-based approaches, and to discuss current barriers to clinical implementation. Testing for the classical inherited thrombophilias, such as the deficiencies of natural anticoagulants antithrombin, protein C and S and the Factor V Leiden variant and the G20210A of Factor II could improve risk stratification and therapeutic decisions in VTE, although their role in VTE management remains controversial. The knowledge regarding genetic susceptibility for VTE progressed in the last two decades, beyond the classical thrombophilias, thanks to the evolution from single-gene Sanger sequencing to genome wide sequencing (GWAS) and next generation sequencing. GWAS has allowed to construct polygenic risk scores (PRS) combining the effects of multiple single-nucleotide polymorphisms. PRS could significantly improve VTE risk prediction beyond clinical factors. The 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 VTE event, being associated

with variants such as those of kininogen 1 and fibrinogen. PRS can stratify VTE risk beyond traditional factors in European-ancestry cohorts; recurrence may have a partially distinct genetic / proteomic architecture, but prospective clinical utility remains to be established and integrating this advanced knowledge into clinical practice remains a future challenge in VTE management.

Key words

genome-wide association study, next-generation sequencing, polygenic risk score, recurrence, thrombophilia, venous thromboembolism

Introduction

Venous thromboembolism (VTE) encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE) with estimated annual incidence rates ranging from 0.75 to 2.69 per 1000 individuals in Western countries [1] increasing with age and reaching over 5 per 1000 in subjects 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 a disease due to the interaction between genetic, individually acquired and environmental factors. This review first outlines classical thrombophilias and current controversies in thrombophilia testing, then summarizes recent GWAS and PRS advances, and finally discusses emerging data on the genetics of VTE recurrence and the challenges of clinical implementation.

Genetics of VTE and thrombophilia

The genetic hereditary component of VTE was evaluated in studies of families, twins, siblings, and estimated to be in the range of 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 favouring VTE started in 1965, when antithrombin (AT) deficiency was first described by Olav Egeberg in a Scandinavian family in which numerous individuals had 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 shown to be rare with prevalence rates ranging from 0.2–2 per 1000 in the overall population [13-14] Subsequently PC was purified from bovine plasma by Johan Stenflo in 1976 and it was called C because 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 coagulation was not understood until Griffin et al[16] associated low levels of plasma PC with VTE in a family study in 1982 [16]. In 1976, Di Scipio et al[17] purified a new vitamin K-dependent plasma glycoprotein which they named protein S (PS) referring to its isolation and characterization in the city of Seattle [17], but it was only in 1984 that Schwarz et al[18] described hereditary PS deficiency as associated with the risk of VTE in a family [18]. Both PC and PS deficiency are rare defects with an estimated prevalence of 3 and 1 per 1000 subjects in the general population, respectively [19].

The loss of function mutations in the SERPINC1, PROC, and PROS1 genes are associated the defects of the natural anticoagulants AT, PC and PS, respectively, with several hundreds of mutations described for each gene [20]. The nature and the functional consequences of the different defects explain to the heterogeneity of the clinical phenotype. These variants are very rare, as a result the 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 rare mutations of natural anticoagulants with loss of function to common gain of function polymorphisms in 1993, when Dahlbäck et al[23] described the resistance to activated protein C (APC-resistance) [23] as a common and strong risk factor for VTE [24]. Subsequently in 1994, Bertina et al[25] from Leiden showed that the cause of inherited APC-resistance was a single mutation (factor V Leiden, rs6025) in the factor V gene in the majority of cases [25-26]. The Arg506 to Gln mutation is situated in the part of the gene encoding for one of the three cleavage sites in factor V (Arg306, Arg506, and Arg679), where PC inactivates factor Va. As a result, factor V Leiden is resistant to the inactivation by PC thus resulting in a gain, and not a loss, of function [26-29]. The risk of thrombosis is 5-fold in heterozygotes, and 50-fold in homozygotes [26-29]. The description of APC-resistance and factor V Leiden transformed hereditary thrombophilia into a common disorder. In fact, factor V Leiden has a prevalence of 5–10% in the general population among Caucasians and it is found in 20–30% patients with VTE and in approximately 50% of patients within thrombophilic families [26-29]. Other rarer variants of factor V which carry resistance to PC have been also 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 gene (Factor II). This polymorphism is associated with increased 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 almost only found in Caucasians. 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 factor V Leiden variant. However, the risk for VTE has been reported to be 30 times increased for homozygotes of the G20210A prothrombin mutation [31,32].

Thrombophilia testing

The mutations causing inherited deficiencies of AT, PC and PS can be assessed routinely in the specialized coagulation laboratory with the detection of decreased plasma levels by immunological assays (quantitative defects or type I deficiency), while functionally abnormal protein molecules are associated with qualitative defects or type II deficiency [31]. However, the genetics of the defects of natural anticoagulants are usually not routinely detected except for specialized research laboratories. On the contrary, the detection of the single nucleotide mutations of factor V Leiden and of the G20201A mutation of prothrombin have become largely available also in non-specialized coagulation laboratories [33]. Factor V Leiden can also be detected with the laboratory phenotype test of activated protein C (APC) resistance and can be confirmed with a genetic analysis; in some cases, only the genotype is determined with molecular analysis without the phenotypical APC resistance test [34]. Differently from factor V Leiden, the G20210A prothrombin mutation can only be detected with a genetic analysis. Other factor V variants different from FV Leiden can determine APC resistance but they are not tested routinely, even in cases which are positive for APC resistance but negative for factor V Leiden [33]. Other genetic causes of thrombophilia, such as antithrombin resistance, factor VIII and factor IX 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 and fibrinogen can be considered in a thrombophilia panel, although there are limited data in large cohorts and genetic basis of these increased levels are only partially known [35].

In clinical practice, nowadays, the panel routinely employed for screening of includes the search for the defects of natural anticoagulants AT, PC and PS as well as the factor V Leiden and G20201A prothrombin mutations. These are defined as classical thrombophilias [31]. However, their clinical utility has been debated for many years. Thrombophilia testing does not

encompass the complexity of the pathophysiology of VTE and its role in guiding the management of VTE remains controversial [34]. There are limited and almost non-existent data on clinical usefulness and benefits of testing for primary and secondary prevention of VTE based on thrombophilia status alone [34,36]. Guidelines of the American Society of Hematology on thrombophilia testing do not recommend universal testing, but only in cases when a positive result would change patient-management [36] albeit with low-certainty evidence for the lack of high-quality outcome data [36]. However, a survey of 82 laboratories adhering to the International Society on Thrombosis and Haemostasis external quality control schemes on thrombophilia testing [33] has shown that classical thrombophilia testing is commonly performed. Laboratories perform plasma-based thrombophilia testing, but 42% only in case of requests from thrombosis/hemostasis specialists, in patients without anticoagulant treatment, or patients with a strong personal of familial history of VTE. In addition, testing is not always performed according to published guidelines with often inadequate adoption of reference intervals from manufacturers or from the literature. Genetic testing is mostly restricted to single-variant testing [33].

For clarity, the principal inherited classical thrombophilias, 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 antithrombin deficiency, and homozygous protein C or protein S deficiency, which are typically associated with the greatest thrombotic burden, as well as the acquired thrombophilia such as antiphospholipid antibody syndrome. Moderate-risk thrombophilias include combined hereditary defects, homozygous factor V Leiden or prothrombin G20210A, and heterozygous protein C or protein S deficiency. In contrast, isolated heterozygous factor V Leiden or prothrombin G20210A are generally considered low-risk

thrombophilias. This pragmatic classification might help to guide the intensity of counselling, prophylaxis in high-risk situations, and decisions around continued anticoagulation in selected patients (Table 2).

The most recent recommendations on the use of thrombophilia testing published by the American Society of Hematology [36] are summarized and compared with those of the International Consensus Statement (ICS) [37] in tables 3, 4 and 5. These two documents differ for their methodological design. The American Society of Hematology (ASH) guidelines were produced by a multidisciplinary panel with the adoption of the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach [36]. The International Consensus Statement is not strictly a guideline, being a consensus, as the quality of evidence in this area is low. As a result, the most recommendation by ASH are conditional and based on very low certainty in evidence.

When does thrombophilia testing change 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 American Society of Hematology (ASH) guidelines [36], thrombophilia testing may be considered in selected clinical scenarios in which the result is likely to modify management, including: (i) patients with VTE at a young age and a strong family history of thrombosis, particularly when high-risk deficiencies (antithrombin, protein C, or protein S) are suspected; (ii) women with a history of VTE who are considering pregnancy or estrogen-containing contraception. In case of women planning pregnancy and with a family history of VTE and thrombophilia, selective testing for thrombophilia known in the family is suggested

to decide ante-partum and post-partum thromboprophylaxis. Women with known homozygous FV Leiden, or combination of FV Leiden and prothrombin gene mutation or antithrombin deficiency should receive antepartum and post-partum thromboprophylaxis. In case of known protein C of preotein S deficiency in the family, testing is left to physiscinas' discretion to guide antepartum thromboprophylaxis. However, in case of positive testing for protein C or protein S deficiency , there is a suggestion for post-partum thromboprophylaxis. In addition. In case of known combination of FVL Leiden and prothrombin gene mutation or antithrombin deficiency in second degree relatives, testing for the thrombophilia known in the family is suggested as well as post-partum thromboprophylaxis in women with thrombophilia. Women considering estrogen containing contraceptives or hormone replacement therpay. There is a strong recommendation to avoid testing women in the general population and testing for thrombophilia only in women in whose family proteian C , S or antithrombin is known and avoid estrogen containing contraceptives or hormone replacement therapy in those with thrombophilia; (iii) individuals with VTE in atypical sites (e.g., splanchnic or cerebral veins); (iv) selected cases in which identification of a high-risk thrombophilia may influence decisions 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 modify therapeutic strategy [36]. Importantly, the presence of common variants such as factor V Leiden or prothrombin G20210A mutation rarely changes the duration of anticoagulation after a first 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 antithrombin, protein C, and protein S [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 (GWAS) have enabled systematic exploration of the polygenic architecture of VTE [38]. GWAS are a genome-wide analysis of genotypes that can be measured using different technologies — for example, whole-genome sequencing (WGS) or genome-wide single-nucleotide polymorphism (SNP) arrays plus imputation. However, most GWAS are still performed using data from SNP arrays [38]. GWAS involve the testing of thousands up to millions of genetic variants across the genomes of many subjects to identify genotype–phenotype associations. As a result, they require the availability and access to large biobanks storing large numbers of DNA samples with related clinical data such as the Million Veteran Program (MVP), the UK Biobank (UKB), and FinnGen. Such biobanks have allowed to associate millions of genetic variants to thousands of human phenotypes (or traits), as well as molecular phenotypes such as transcriptomics and proteomics [39,40].

GWAS have substantially changed the field of complex disease genetics over the past decades [41-45]. Since 2005, when the first GWAS for 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 the disease susceptibility for several of diseases including VTE [44,45]. Several new VTE disease loci have been described and previously discovered VTE loci have been confirmed by GWAS studies [46].

However, it was then realized that GWAS loci typically have small effect sizes with relative risks between 1.0 and 1.5 and can be associated with only a modest proportion of trait hereditability [38]. In addition, GWAS are limited by an important burden of multiple testing with of a high level of significance to account for the multiple tests, (e.g. increasing the sample size) and thus the cost of testing. GWAS can explain only a modest fraction of the missing heritability, probably due to the stringent threshold of significance. Beyond stringent 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 non-additive genetic effects, which are not fully captured by common-variant GWAS models [47, 48]. Another problem of GWAS is that rare variants will not be detected, such as those causing deficiencies of AT, PC, and PS even very large GWAS studies [47,48]. In contrast, GWAS predominantly detect common variants with small effect sizes, which explain only a limited proportion of the total phenotypic variance and contribute to the phenomenon of "missing heritability" [38]. As a result, the clinical predictive value of GWAS per se is quite limited. In addition, the common variants detected may be related to genes of components non 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 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 VTE

Recently, Ghouse et al[49] published the results of a GWAS meta-analysis of six 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 six studies included samples from biobanks such as the Copenhagen Hospital Biobank Cardiovascular Disease Cohort (CHB-CVDC), the Danish Blood Donor Study (DBDS), deCODE, Intermountain Healthcare, UKB, FinnGen and the MVP, comprising approximately 9.6 million sequence variants [49]. Ninety-three loci met conventional genome-wide significance ($P < 5 \times 10{-}8$), of which 62 were novel, e.g. not overlapping with a previously reported locus for VTE.

They also investigated whether PRS could identify at-risk individuals and whether PRS could increase or mitigate the risks risk associated with known thrombophilia genes (that is, factor V Leiden and prothrombin mutations) and traditional risk factors [49]. The authors derived the PRS for VTE 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 VTE PRS could effectively identify both high- and low-risk individuals. Those individuals within the top 0.1% of PRS distribution had a VTE risk similar to homozygous or compound heterozygous carriers of the variants G20210A in factor II and in factor V Leiden. They also found that factor II and factor V mutation carriers in the bottom 10% of the PRS distribution had a risk similar to that of the general population [49]. If these results are confirmed, current recommendations regarding the testing for classical thrombophilias (see Tables 1-3) should be regarded with caution. PRS could improve individual risk prediction beyond that of genetic and clinical risk factors. The authors calculated the ten-year risk of VTE according to PRS and clinical (sex, age, smoking status) risk factors. In addition to relative risk estimates, the authors 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 polygenic risk scores 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 al[52] 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 studies and Mendelian randomization (MR) in which genetic variants corresponding to modifiable exposures (e.g., 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 one novel gene locus (GPR149). Among all variants known to be associated with 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 factor XI, factor VIII, von Willebrand factor, histoblood 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 subgroups[53]. The study findings challenge the understanding of VTE and VTE 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 (factor XI, BGAT, von Willebrand factor, and factor VIII) were found to be linked to VTE recurrence [52,53]. This would imply that the risk of recurrent VTE is genetically and biologically distinct from initial VTE risk, revolutionizing 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 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 variant SLC4A1 p.Glu40Lys was associated with a threefold increased risk of recurrence in patients with PE but not in those with DVT—which reinforces the emerging notion that PE and DVT may differ at the molecular level [53]. These findings challenge the conventional notion that thrombophilia testing is of limited utility while genetics—when scaled appropriately and interpreted through updated robust analytic frameworks—can explain pathways which 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 in order to personalize anticoagulation decisions in 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 that distinguishes between O1.1 and O1.2) in 1576 VTE cases and 17 535 ancestry-matched controls, evaluated the effects of ABO haplotypes on VTE risk and recurrence [54]. In east Asians, the rs1053878-A allele is consistently co-inherited 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 a ∼1.4-fold increased risk of VTE ($p = 5.2 \times 10-20$) and a ∼1.7-fold increased risk of recurrence ($p = 0.023$), compared to the O1.1 group.[54]

In a Thai case–control genotyping study (122 VTE cases; 87 matched controls), seven SNPs showed significant associations with VTE, including five risk alleles (PROC, ABO, FGG, factor XI, HIVEP1) and two protective alleles (factor V, TGFB2) [55]. A combined polygenic risk score integrating genetic and clinical factors predicted recurrence, particularly in unprovoked VTE, with a >3-fold higher recurrence risk. These findings provide population-specific evidence for VTE genetic susceptibility in Thais and support PRS-informed recurrence stratification using a scalable, cost-effective MassARRAY SNP panel [55]. As the tools of genomic medicine become more accessible, more research is required to incorporate these findings into clinical practice in order to personalize anticoagulation decisions in VTE. Current clinical models—such as HERDOO2, DASH, 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 from prolonged anticoagulation or experience recurrent thrombosis after discontinuation. The findings by Munch et al[53] demonstrated that the genomic architecture of VTE recurrence is distinct from that of the first event, identifying multiple loci and proteins (e.g., GPR149/MME, KNG1, FGG, factor XI, factor VIII, vWF) associated with recurrence and highlighting the value of polygenic risk scores (PRS) to stratify recurrence risk. Integrating these genetic determinants with clinical features and functional biomarkers (e.g., thrombin generation, D-dimer, factor VIII) could provide a robust individualized estimate of recurrence risk and support personalized discontinuation of anticoagulant therapy.

Next generation sequencing (NGS)

Another evolution of genetics is the development and availability of several so-called next generation sequencing (NGS) or High Throughput Nucleotide Sequencing platforms. NGS allow the generation of fast, inexpensive and accurate genomic information, as reviewed by Cunha et al[56]. NGS studies could either employ whole exome sequencing (WES) or whole genome sequencing (WGS), or NGS could be used for resequencing of targeted candidate gene [57,58]. NGS allows 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 and even if studying mutation enrichment in genes large studies will be necessary. Rather, its use may be justified in selected high-yield clinical scenarios, such as patients with early-onset thrombosis, strong familial clustering, severe deficiency of natural anticoagulants with inconclusive standard testing, 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 pre-test 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 PRS with established clinical predictors and functional biomarkers, such as D-dimer, factor VIII, and thrombin generation parameters, to determine their incremental predictive value and clinical utility [49,52]. Cross-ancestry validation and recalibration of PRS 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 anticoagulation therapy and improve patient-centered outcomes after a first VTE episode [36, 49]. Future investigations should also assess net clinical benefit and cost-effectiveness of genomic risk stratification within real-world healthcare systems. Finally, development of standardized implementation frameworks and adherence to established reporting standards for PRS 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 healthcare 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

GWAS 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 of PRS that may complement traditional clinical risk assessment, in particular in subjects with 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 to define the duration of anticoagulant treatment in patients with a first episode of VTE, However, PRS do not account for gene-environment interactions and life-style characteristics [35]. In addition, a strong family history of VTE , free of any classical inherited thrombophilias, in a subject who develops VTE is per se' an index of a high risk for VTE, but PRS combined with clinical date could better identify those subjects with a higher risk of recurrence and thus determine the optimal duration of anticoagulant treatment.

However, despite promising advances, the translation of genomic findings into routine clinical practice requires further prospective validation, standardized implementation strategies, and the demonstration 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.

Article information

Acknowledgements None

Funding None

Conflict of interests None

AI statement Artificial intelligence was not used to write the article.

How to cite Cosmi B, Gerotziafas G, Marschang P, et al. Inherited thrombophilia and polygenic risk scores in venous thromboembolism: from classical testing to genomic risk prediction. Pol Arch Intern Med. 2026; XX: 17287. doi:10.20452/pamw.17287.

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Table 1 Classical inherited thrombophilias: prevalence, relative risk of first venous thromboembolism, and diagnostic modalities				
Variant / Deficiency	**Prevalence in 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 ± SERPINC1 sequencing	High-risk, rare; strong family aggregation
Protein C deficiency	~0.2–0.4% [17]	5–10-fold [17,18]	Functional + antigenic assay ± PROC sequencing	Variable penetrance; acquired reductions common
Protein S deficiency	~0.03–0.13% [17]	5–10-fold [17,18]	Free PS antigen ± PROS1 sequencing	Influenced by pregnancy, OCPs, inflammation
Factor V Leiden (heterozygous)	5–10% (Caucasians) [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 risk; often combined with FVL
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; FVL, factor V Leiden; OCPs, oral contraceptive pills; PCR, polymerase chain reaction; VTE, venous thromboembolism				

Table 2 Classification of thrombophilia according to VTE risk		
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 (FII) G20210A	Protein C deficiency (heterozygous)	Prothrombin (FII) G20210A (heterozygous)
Protein C deficiency (homozygous)	Protein S deficiency (heterozygous)	
Protein S deficiency (homozygous)		

a "Combined hereditary thrombophilia" refers to the coexistence of ≥2 inherited thrombophilic defects, such as Factor V Leiden plus prothrombin (FII) G20210A, or a high-risk defect (eg, antithrombin, protein C, or protein S deficiency) combined with another inherited thrombophilic abnormality

Table 3 Recommended thrombophilia testing according to the clinical context (provoked and unprovoked) and targeted work-up as published by American Society of Hematology guidelines on thrombophilia testing [36] in comparison with the International Consensus Statement (ICS) [37]

Clinical scenario	**Who to test**		**What to test (suggested panel)**		**Evidence / strength (if stated)**		**Rationale / impact on management**	
Unprovoked VTE (index event)	**ICS**	**ASH**	**ICS**	**ASH**	**ICS**	**ASH**	**ICS**	**ASH**
	First episode of unprovoked VTE <50 years, with or without family history	Do not test	Inherited thrombophilia panel[a] ± antiphospholipid antibodies (aPL)	No tests	----	**Low / Conditional**	May help in recurrence risk assessment, family counselling, and selected management decisions	Testing does not help decisions on duration of anticoagulation as guidelines recommend long term anticoagulatio, 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 choice of anticoagulant (eg, APS considerations)	

Provoked VTE	**VTE provoked by non-surgical major transient risk factor**	Test for thrombophilia	Inherited thrombophilia panel[a] (selective)	Thrombophilia panel	**----**	**Low / Conditional**	May support risk stratification when provoking factor is not surgical/major operative	Indefinite anticoagulant treatment for patients with thrombophilia
	VTE provoked by minor risk factor	—	**aPL testing**	—-	**Low / weak**	**—**	May alter antithrombotic choice/duration if APS idientified	---
	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 (± additional variants per local practice). Testing should be timed appropriately (avoid acute thrombosis phase and anticoagulant interference when possible)								

Table 4 Recommended thrombophilia testing according to the clinical context (women-specific triggers) and targeted work-up as published by American Society of Hematology guidelines on thrombophilia testing [36] in comparison with the International Consensus Statement (ICS) [37]

Clinical scenario	**Who to test**		**What to test (suggested panel)**		**Evidence / strength (if stated)**		**Rationale / impact on management**	
Women-specific triggers	**ICS**	**ASH**	**ICS**	**ASH**	**ICS**	**ASH**	**ICS**	**ASH**
	—	Provoked by pregnancy or post-partum	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 use of COC	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)

Table 5 Recommended thrombophilia testing according to the clinical context (different VTE conditions) and targeted work-up as published by American Society of Hematology guidelines on thrombophilia testing [36] in comparison with the International Consensus Statement (ICS) [37]

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, splanchic thrombosis	aPL; consider MPN panel / JAK2; consider PNH if blood abnormalities	1-In settings when anticoagulation would otherwise be discontinued after primary short-term treatment: test 2- In settings when anticoagulation would otherwise be continued indefinitely: do not test	**Low / weak**	**Low / Conditional**	Unusual sites raise suspicion for 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 counts	--
Catastrophic / fulminant presentations	Acute multiple thrombotic events with	Not considered	aPL testing	--	**Low / strong**	--	Diagnosis drives urgent, specific treatment strategies	--

	organ failure suggestive of CAPS		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)								

Table 6 Recommended thrombophilia testing according to the clinical context (family based testing and cancer setting) and targeted work-up as published by American Society of Hematology guidelines on thrombophilia testing [36] in comparison with the International Consensus Statement (ICS) [37]

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 (1st/2nd degree; multiple relatives; young index case)	Asymptomatic Individuals with a family history of VTE and known thrombophilia Presenting with a minor transient provoking risk	Targeted inherited thrombophilia testing guided by family defect[a]	1-Strategy #1 selective testing for the thrombophilia known in the family but if Heterozygous FVL or eterozygous	--	**Low /conditional**	Informs counselling, avoidance of high-risk exposures, and prophylaxis in high-risk situations	Use thromboprophylaxis In individuals with thrombophilia

		factor (e.g. immobility or minor injury, illness or infection)		PGM do not test 2- Strategy #2: doing a thrombophilia panel: if Heterozygous FV or heterozygous PGM: no panel 3- Protein C, S, or antithrombin deficiency: test for all hereditary thrombophilias				
	Asymptomatic first-degree relatives of probands with **protein C, protein S, or antithrombin deficiency**, when results would change management/life choices	Asymptomatic Individuals with a family history of thrombophilia but no VTE	Targeted testing for the known deficiency	1-If heterozygous FV or heterozygous PGM: no testing 2-Protein C, S, or antithrombin deficiency in first degree relatives: test for	**Low / weak**	**Low / Conditional**	Selective testing only when it will meaningfully influence decisions (eg, pregnancy, hormone-based therapies, surgery)	Use thromboprophylaxis In individuals with thrombophilia

				thrombophilia known in the family 3- if in second degree: do not test				
Cancer setting	Ambulatory / hospitalized cancer patients at **low–moderate VTE risk** but with **first-degree family history of VTE**	Ambulatory patients with cancer who are classified to be at low or intermediate risk for VTE, who have a family history of VTE in first-degree relatives	Selective inherited thrombophilia testing[a]	Doing a thrombophilia panel Test for all hereditary thrombophilia (panel)	--	**Low / Conditional**	May refine prevention strategy in borderline-risk patients	Use thromboprophylaxis in individuals with thrombophilia
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)								

Short title: Inherited thrombophilia and polygenic risk in VTE