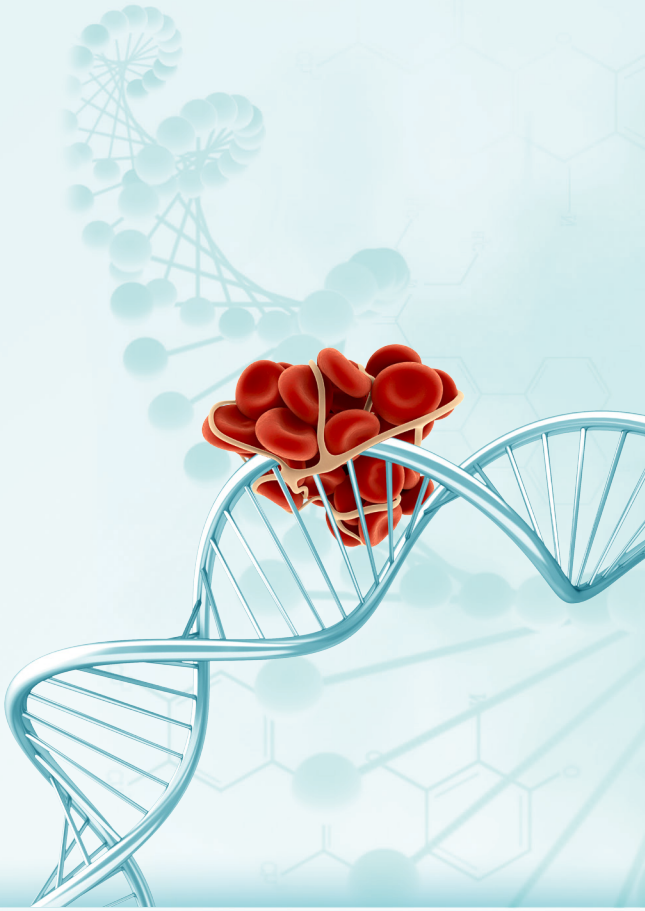


THROMBO inCode

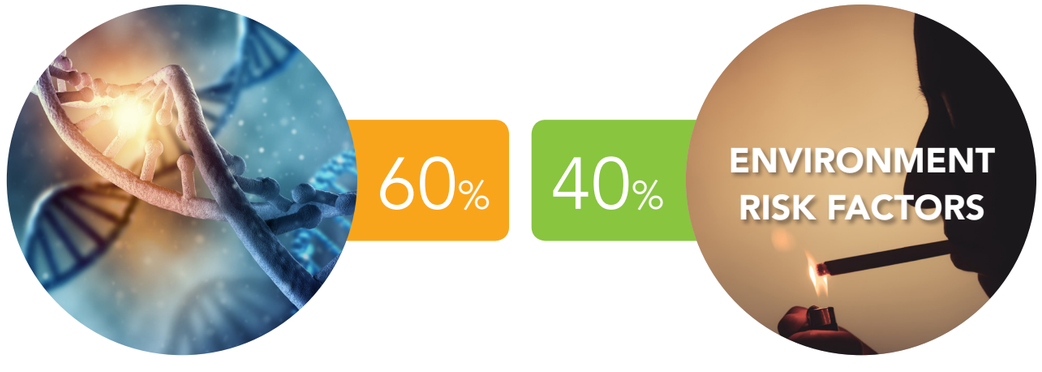
More answers for managing
genetic thrombophilia

GEN inCode

HEREDITARY THROMBOPHILIA

Hereditary thrombophilia is a genetic predisposition to venous thromboembolism (VTE).

It is due to several genetic[1] mutations that alter the clotting cascade, increasing individual risk[2] of VTE.

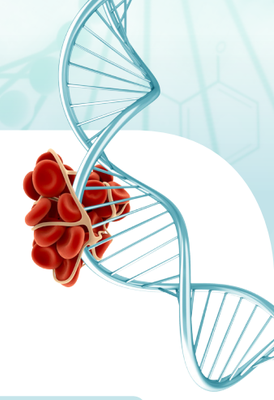


According to the GAIT study, genetics accounts for 60% in the ocurrence of thromboembolic events.[3]

Genetics, along with plasma tests, is key to diagnosing thrombophilia.

Unlike plasma tests, the results of genetic tests are not affected by clinical or pharmaceutical conditions and they don't change over the course of a patient's life.

CURRENT DIAGNOSIS OF HEREDITARY THROMBOPHILIA[4]



PLASMA TESTS	GENETIC TESTING
• Prothrombin time	• Factor V Leiden
• Activated partial thromboplastin time	• 20210 AG PT gene mutation (Prothrombin)
• Antithrombin activity	
• Protein C activity (chromogenic)	
• Free protein S antigen	

The genetic markers analysed today, FV Leiden and Prothrombin, can only diagnose 20% of patients with hereditary thrombophilia.[5]

MORE COMPLETE RESPONSE TO MANAGING THROMBOPHILIA

THROMBO inCode combines:

1. A validated panel[5] of 12 genetic mutations, all of which are causal and functional with a pro-thrombogenic effect on the clotting cascade.

Screening for thrombophilia genetic profile.

2. An algorithm using the patient's genetic profile and medical history/risk factors: gender, age, BMI, diabetes, smoking habits, family history of VTE, hormone-based contraceptives, pregnancy. The different risk levels are calculated based on various combinations of potentially modifiable risk factors.

Calculation of the patient's risk of having a venous thromboembolic event.

THE TOOL FOR GENETIC DIAGNOSIS OF HEREDITARY THROMBOPHILIA AND PREDICTION OF VTE RISK

CLINICAL DATA + DNA SAMPLE*

*Saliva or blood

CLINICAL DATA +

1 GENETIC RESULTS

12 genetic mutations on 7 genes involved in venous thromboembolism, selected based on meta-analysis[3,6] and validated (JAHA).[5]

2 THROMBOSIS RISK SCORE

Exclusive tool only available with Thrombo inCode.
Uses genetic and clinical data to assess thromboembolic risk

3 RECOMMENDATIONS REPORT

Personalised report. Explains the patient's current level of risk and how this can be changed through modifiable risk factors.

- Managing situations that increase risk
- Recommending family study

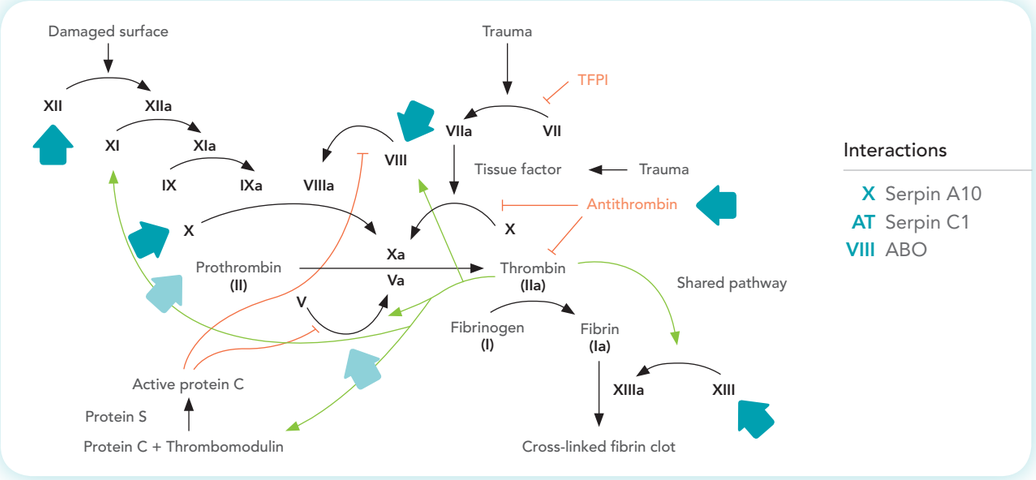
THROMBO inCode

IS AVAILABLE AS A DIAGNOSTIC SERVICE OR LABORATORY KIT

THE PANEL OF 12 GENETIC MUTATIONS

VARIANTS	GENE/PROTEIN MUTATIONS	PREVALENCE	RELATIVE VTE RISK[d]
rs6025 (FV Leiden)	Factor V[7-13]	15-25%	5 (h) / 34 (H)
rs1799963 (Prothrombin)	Factor II[7-9, 14,15]	6-16%	4,20 (h) / 26,4 (H)
rs1801020	Factor XII[16-18]	6%[c]	3,22 (h)
rs8176719	ABO Group[19-21] (A1 carriers)	nd	2,6
rs7853989			
rs8176743			
rs8176750			
rs2232698	Serpin A10[22]	4,4%	3,89
rs121909548	Serpin C1[23]	1,7%	9,75
rs118203906 (FV Cambridge)	Factor V[7-13]	nd	5 (h) / 34 (H)
rs118203905 (FV Hong Kong)			
rs5985	Factor XIII[8,24,25]	2%[c]	0,8

(h): Heterozygote / **(H)**: Homozygote / **c**: Zygosity / **d**: Data obtained from bibliography and meta-analyses
VTE: Venous thromboembolism



VALIDATION STUDY[5]

Published in the JAHA (Journal of the American Heart Association) • October 2014

AIM To analyse the predictive capacity of ThromboinCode to assess a subject's risk of having a thromboembolic event.

STUDY POPULATION

SANT PAU – Spain	MARTHA – France
• 248 cases – 249 controls	• 477 cases – 477 controls
• Age: 49.0/47.1	• Age: 44.2/43.9
• Males: 44.0/44.6%	• Males: 41.5/41.5%
• Representative sample of the general population (Caucasian)	• Sample population (Caucasian) enriched with PT and FVL

Comparison of discriminative and predictive capacity of the 12 mutations in Thrombo inCode (GRS2) with:

GRS1 V Leiden factor and 20210 AG Prothrombin gene mutation (current gold standard for diagnosing hereditary thrombophilia)

GRS3 Risk score developed by Dr Rosendaal's thrombophilia research group (Leiden University)

GRS4 Combination of GRS2 and GRS3, taking into account genetic mutations associated with the development of venous thromboembolism, according to the literature.

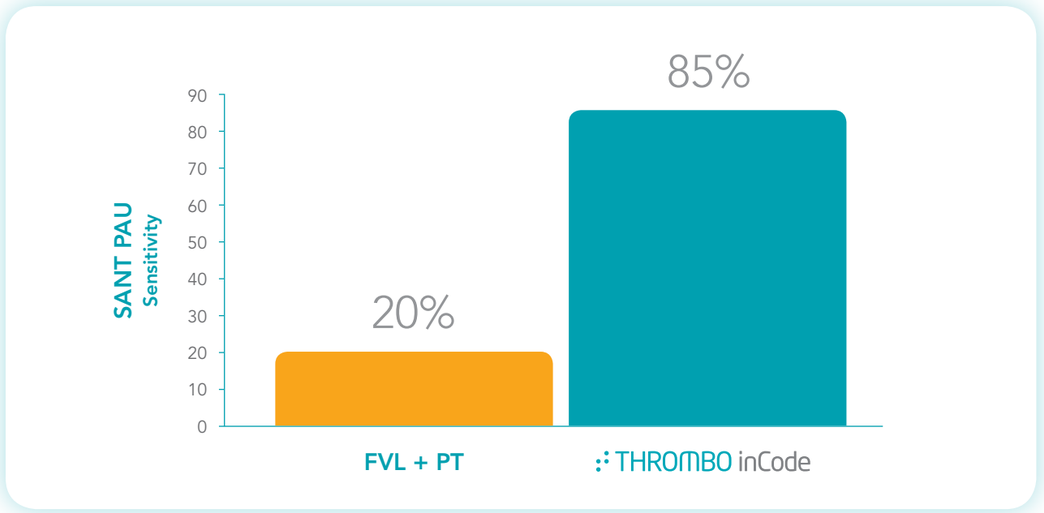
*GRS: Genetic Risk Score

VALIDATION STUDY[5] RESULTS

THROMBO inCode

- **SIGNIFICANTLY IMPROVES** the ability to predict a VTE event based on family history (AUC 0.701 vs 0.589).
- **SURPASSES** FVL + PT combination in ability to predict a VTE event.(AUC 0.68 vs 0.57) and increases sensitivity from 20% to 85%.
- Adding **more variables does not increase** the predictive capacity of Thrombo inCode.

Clinical utility (measured in terms of sensitivity) of TiC* compared to FVL + PT in SANT PAU population



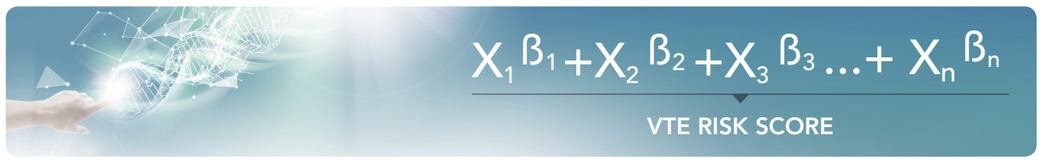
*Tic: Thrombo inCode / Graph adapted from reference text 10

ALGORITHM TO CALCULATE VENOUS THROMBOEMBOLISM RISK SCORE

This algorithm allows us to calculate a person's probability of having VTE depending on their genetic, sociodemographic and clinical characteristics.

- It weighs each value taking into account its associative power (OR*). Each one has its own specific weight.
- Most algorithms used today only take into account clinical data, while **Thrombo inCode uses both genetic and clinical data.**
- The risk assessment also takes into account specific conditions that may change over time, allowing it to be recalculated whenever necessary.

*OR: Odds ratio



Each variable (x1, x2, x3, etc.) in the algorithm corresponds to clinical or genetic conditions assessed in our algorithm:

- Genetic mutations (PT, FVL, FXII, FXIII, etc.)
- Age, gender, smoking habits, diabetes, etc.

Each variable is given its own specific weight (β_1, β_2, β_3, etc.). This ensures it not only takes into account the presence of the risk factor but also quantifies its degree of risk.

ALGORITHM TO CALCULATE VENOUS THROMBOEMBOLISM RISK SCORE

FICTITIOUS PATIENT

RISK SCORE BASED ONLY ON CLINICAL PROFILE AND FVL+PT 3,03		
GENDER	H:1 M:2	2
AGE	Years old	56
SMOKER	NO: 0 YES: 1	1
DIABETES		0
FAMILY HISTORY		1
PREGNANCY		0
CONTRACEPTION		0
BMI	Kg/m^2	27
PROTHROMBIN (FII)	NO: 0 Hetero: 1 Homo: 2	0
FV LEIDEN		0

RISK SCORE BASED ON THROMBO INCODE 7,52		
GENDER	H:1 M:2	2
AGE	Years old	56
SMOKER	NO: 0 YES: 1	1
DIABETES		0
FAMILY HISTORY		1
PREGNANCY		0
CONTRACEPTION		0
BMI	Kg/m^2	27
PROTHROMBIN (FII)	NO: 0 Hetero: 1 Homo: 2	0
FV LEIDEN		0
FV CAMBRIDGE		0
FV HONG KONG		0
FXII		2
FXIII		0
SERPIN C1		0
SERPIN A10		0
A1 CARRIER		1

PATIENT CANDIDATE PROFILES

- Patients with a **family history** of VTE or hereditary thrombophilia.
- Patients with a **personal or family history** of VTE with **temporary conditions** that increase the risk of thrombosis.*
- Family members of an individual diagnosed with hereditary thrombophilia **(family study).**

- Patients being treated for venous thromboembolism to assess the **risk of re-thrombosis.**
- Patients with a VTE profile that suggests **hereditary thrombophilia**: VTE in patients under 45, recurring VTE, in unusual vascular areas, etc.
- **Women with issues of infertility** (repeated miscarriages/implantation failures to implant) with no identified cause or suspected thrombophilia.

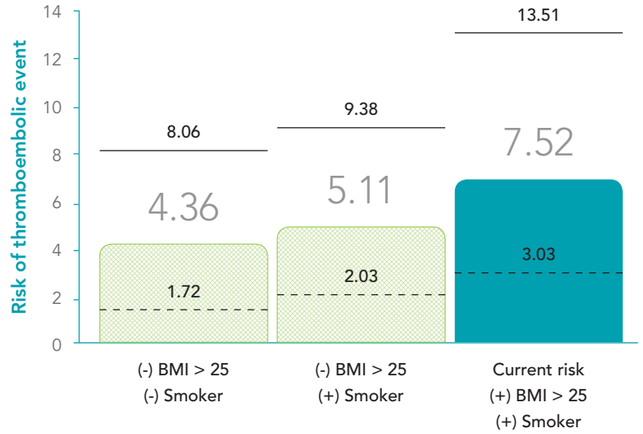
* Such as: pregnancy, hormone-based contraception, hormone-replacement therapy, major surgery, paralysis or trips over 5 hours.

THROMBO INCODE REPORT

RISK SCORE AND MODULATION OF THE RISK

Assessment of risk for having venous thromboembolic events

According to the clinical and genetic information provided, your patient's current risk of having a thromboembolic event is 7.52.

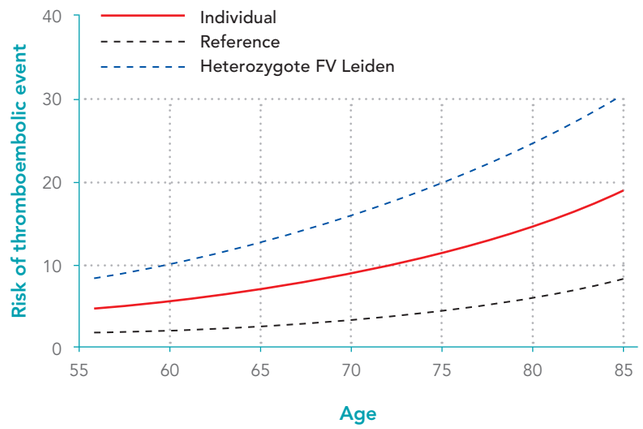


BMI: Body Mass Index

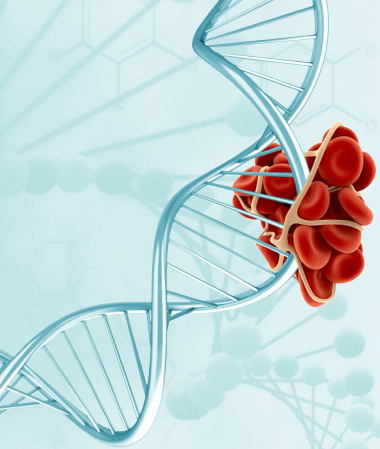
The patient's risk is compared to:

- The risk level of a similar patient without any additional genetic mutations (dotted line).
- The risk level of a patient with a similar clinical profile that is a heterozygote FVL carrier (solid line).

Evolution of patient's risk over time



The patient's evolution of risk is compared to the same 2 theoretical profiles mentioned before.



THROMBO inCode

DIAGNOSIS OF GENETIC THROMBOPHILIA PROFILE
Greater sensitivity in detecting pro-thrombotic genetic mutations[4]

RISK SCORE FOR HAVING A VENOUS THROMBOEMBOLIC EVENT
Overall risk assessment using both genetic and clinical data

PERSONALISED RECOMMENDATIONS REPORT
Support in managing VTE risk of patients and their family members

COST/BENEFIT STUDY FOR VTE RISK ASSESSMENT
Thrombo inCode is the predominant option (more effective and affordable than FVL and PT)[26]

GEN inCode

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