THROMBO inCode

Diagnosis, risk assesment
and management of
hereditary thrombophilia

GENinCode

THROMBO inCode

Thrombo inCode® is a clinically validated gold-standard test for the diagnosis, risk assessment and management of hereditary thrombophilia.

Thrombo inCode® uses both a genetic panel and a clinical-genetic algorithm to diagnose a patients hereditary thrombophilia profile, which combined with their clinical risk factors provides a comprehensive risk assessment of their likelihood to develop a VTE event.

Thrombo inCode® provides clear, clinically actionable results that enable preventive measures to be taken, including prophylactic treatment if necessary, to minimise the risk of developing a VTE.

Furthermore, Thrombo inCode® provides information to support the management of the patient's thrombotic risk in the medium/long term.

1. Venous Thromboembolism (VTE): a pathology with clinical-genetic causality
2. The need to expand the genetic analysis of hereditary thrombophilia
3. Scientific evidence and validation studies of Thrombo inCode®.
4. Thrombo inCode®: A clinical-genetic test for Trombophilia diagnosis and VTE risk assessment
5. Clinically actionable recommendation report
6. Candidate patients profile
7. Patient data integration and online management

1. Venous Thromboembolism (VTE): a pathology with clinical-genetic causality

Hereditary Thrombophilia

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

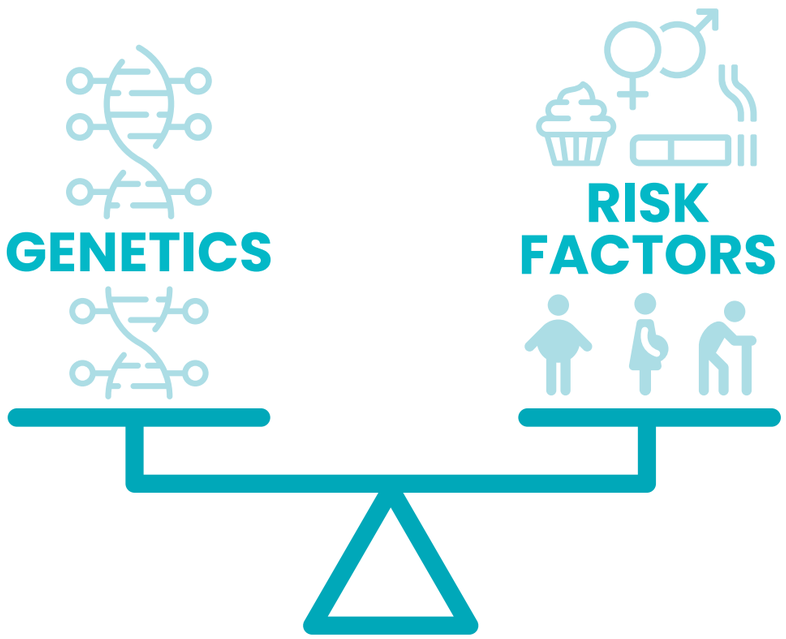
Certain genetic variants [1] alter the coagulation cascade, increasing the individuals risk of VTE [2].

Interaction of Risk Factors

The development of a Venous Thromboembolism (VTE) episode is influenced by:[3]

- A thrombophilic genetic profile
- External risk factors; whether modifiable or not

Several studies show that the heritability risk of VTE is due to a 45-60% genetic component. [3,6]



2. The need to expand the genetic analysis of hereditary thrombophilia

Diagnosis of Hereditary Thrombophilia

The use of Factor V Leiden (FVL) and the G20210A variant in the prothrombin gene (PT), for the diagnosis of inherited thrombophilia, only identifies 20% of patients having developed a VTE episode. [7]

GWAS studies have demonstrated the association of several genetic variants with VTE, with a polygenic risk equivalent to that of the FVL and PT variants. [8]

Several studies show that the incorporation of appropriately selected genetic variants into Genetic Risk Scores (GRS) has a positive, strong and linear association with VTE risk. [9]

Thrombosis risk assessment

As a disease of clinical-genetic causality, the integration of these two factors is crucial for the accurate assessment of VTE risk. [6,9]

This comprehensive assessment provides information that enables the clinician to establish preventative plans and/or suitable treatment. [9]

3. Scientific evidence and validation studies of Thrombo inCode®

VALIDATION STUDY OF THROMBO INCODE FOR RISK PREDICTION [7]

Multilocus Genetic Risk Scores for Venous Thromboembolism Risk Assessment
Soria et al, JAHA oct 2014

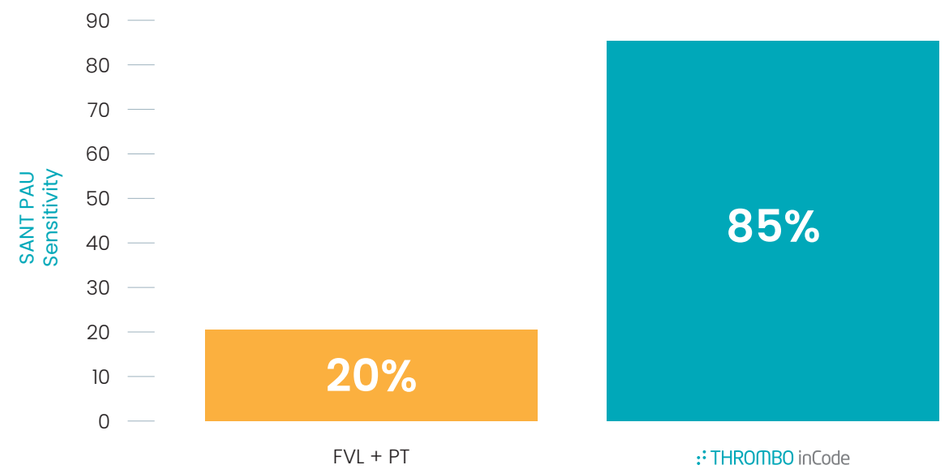
Objective: To analyse the predictive capacity of Thrombo inCode® vs. FVL+PT and other genetic risk scores for developing a thrombotic event.

Multicentric retrospective case-control study. Development and validation in 2 populations:

SANT PAU cohort: 248 cases - 249 controls. Population representative of the general Spanish population (Caucasian).

MARTHA cohort: 477 cases - 477 controls. Population from the South of France enriched in FVL and PT.

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

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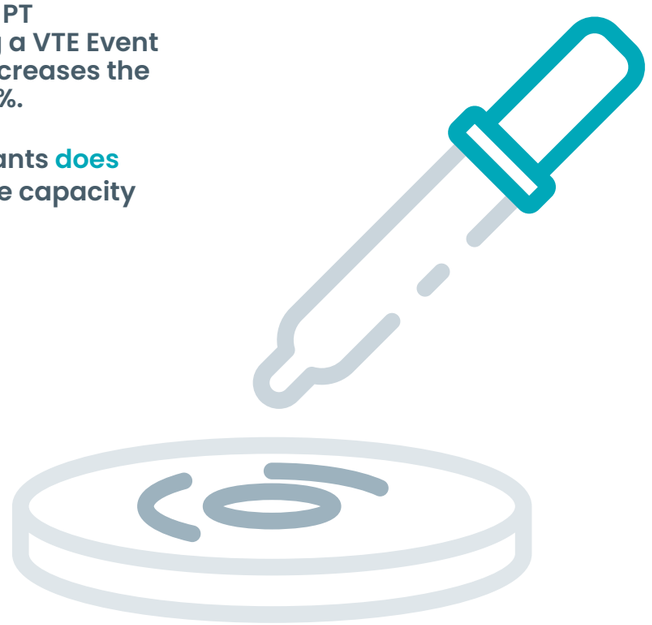
TiC outperforms the FVL + PT combination in predicting a VTE Event (AUC 0.68 vs. 0.57) and increases the sensitivity from 20% to 85%.

The addition of more variants does not increase the predictive capacity of Thrombo inCode®.



THROMBO INCODE® IS THE DOMINANT OPTION VS. FVL + PT IN TERMS OF COST-EFFECTIVENESS FOR VTE RISK MANAGEMENT [37]

Economic Analysis of Thrombo inCode, a Clinical–Genetic Function for Assessing the Risk of Venous Thromboembolism
Rubio-Terrés et al. Appl Health Econ Health Policy 2015

Retrospective case-control study (in 2 populations, total n= 1,451), taking into account only direct health costs (National Health System perspective).

Objective: Conduct a comparative economic study of VTE risk management using Thrombo inCode® or FVL and PT.

Results: Thrombo inCode® proves to be a dominant option (more efficient and less costly than the strategy with FVL and PT) in 100% of the scenarios.The price of Thrombo inCode is between 22 and 66 times lower than the reference ICER*, depending on the population studied).

** (Incremental cost-efficiency ratio)*

NEW VALIDATION OF THROMBO INCODE® FOR VTE RISK PREDICTION [38]

Predictive Ability of a Clinical-Genetic Risk Score for Venous Thromboembolism in Northern and Southern European Populations
Salas et al. Th Open Jul 2021

Multicentre retrospective case-control multicentre study (n= 370)

Objective: To validate the predictive ability of Thrombo inCode® (TiC) for VTE risk assessment in a Northern European population.To compare the predictive ability of Thrombo inCode® with several genetic and/or clinical risk scores, including FVL+PT.

Results: TiC has a higher predictive capacity (statistically significant) vs. FVL+PT, even if the clinical variables analysed in TiC are added to FVL+PT.

TiC identifies 2.5 times more patients with hereditary thrombophilia than FVL+PT (sensitivity 72.3% vs 28.9%).

The incorporation of additional genetic variants does not improve the predictive capacity of TiC.

PREDICTIVE ABILITY OF THROMBO INCODE® IN RECURRENT VTE [39]

A clinical-genetic score for risk assessment of recurrent VTE
Gerotziafas et al. Blood 2016

Retrospective case-control study (n=55), using all genetic variants and clinical variables of Thrombo inCode®.

Objective: To analyse the predictive capacity of a new clinical-genetic risk score for the prediction of recurrent VTE: Thrombo inCode®-Recurrent (TiC-Recurrent)

Results: TiC-Recurrent has an AUC of 0.74 and a sensitivity of 81.8%. These preliminary results demonstrate a good predictive ability of TiC-Recurrent for the identification of patients at risk of recurrent VTE.

USE OF THROMBO INCODE® AS GOLD-STANDARD [40]

Predicting venous thromboembolism risk from exomes in the Critical Assessment of Genome Interpretation (CAGI) challenges
MCInnes et al. Human Mutation 2019

Multicentre restrospective study (n= 103)

Objective: Comparison of the predictive ability of different VTE risk assessment methodologies, including exome analysis and clinical data, in an African-American population.

This study is part of the 5th challenge of the Critical Evaluation of Genomic Interpretation.

The organisation uses TiC ("Soria's model") as the gold-standard method to compare the predictive capacity of the other methodologies used.

Results: TiC obtained an AUC of 0.71 confirming its validity for VTE risk prediction in a new population profile.

4. Thrombo inCode®: A clinical-genetic test for thrombophilia diagnosis and VTE risk assessment

Clinical Risk Score : *8 factors*


Gender


Age


Family History


BMI


Diabetes


Smoking


Prothrombotic Contraceptives


Pregnancy

Genetic risk score : *12 variants in 7 genes*

Related Protein	Variant effect
Factor V [7-13]	Causes resistance to activated protein C (RPCA), with an increased risk of venous thrombosis of 6-8 times in heterozygous carriers and 18 in homozygous carriers. [4, 15, 17, 18-21]
Protrombin (FII) [7-9, 14,15]	Increased plasma levels of factor II, with a risk of venous thrombosis 2-3 times higher than in non-carriers. [16, 17, 4] Specific risk of thrombosis in cerebral venous sinuses (OR=13). [16]
ABO Group [19-21]	Increased risk of venous thrombosis: 2 times higher for non-O groups due to influence on plasma levels of factor VIII and Von Willebrand factor. [7, 26, 27]
Factor XII [16-18]	Associated with a decrease in plasma FXII levels [1, 12, 13], with an increased risk of thrombosis in homozygous carriers.
Factor XIII [8,24,25]	Reduced susceptibility to thrombotic events.
Serpin A10 [22]	3-fold increased risk of venous thrombosis associated with Protein Z Inhibitor deficiency. [2]
Serpin C1 [23]	Antithrombin deficiency characterised by normal antigenic levels, normal anti-FXa activity but reduced anti-IIa activity in the presence of heparin. It confers a 10-fold higher risk of venous thrombosis than non-carriers. [3, 13]

5. Clinically actionable recommendation report

ANAMNESIS + **DNA SAMPLE** BLOOD OR SALIVA

GENETIC DIAGNOSIS OF HEREDITARY THROMBOPHILIA

DUE TO A VALIDATED GENETIC PANEL

CLINICAL DATA **GENETIC PROFILE**

INTEGRATION IN A VALIDATED CLINICAL-GENETIC ALGORITHM

THROMBOSIS RISK SCORE

CALCULATION OF THE PATIENT'S VTE RISK AND COMPARISON WITH:

- SAME CLINICAL PROFILE BUT NO GENETIC LOAD
- SAME CLINICAL PROFILE BUT WITH ONLY FVL (HETEROZYGOUS)

RECOMMENDATIONS

- VARIATION OF RISK BY CORRECTING EXISTING RISK FACTORS
- RECOMMENDATIONS FOR PROPHYLACTIC MEASURES BASED ON THE PATIENT'S RISK PROFILE
- ADDITIONAL MEASURES IF NECESSARY: REFERRAL, FAMILY STUDY, ETC.

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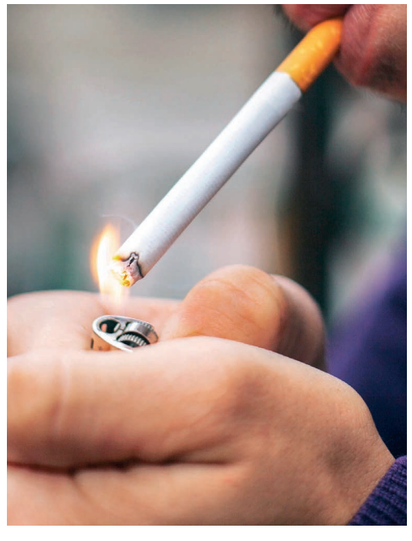
6. Candidate patients profile

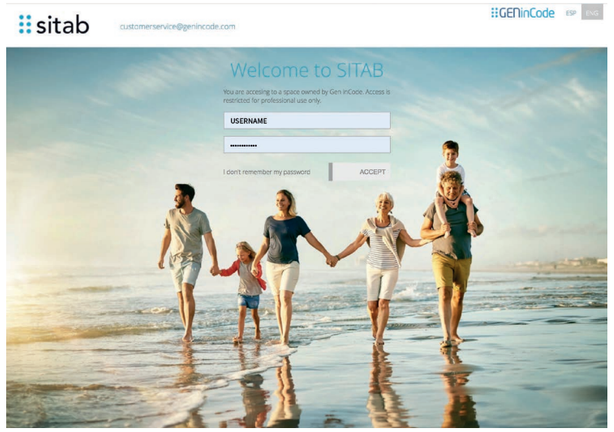
- Patients with a personal history of VTE, especially in the presence of transient conditions that increase the risk of thrombotic events.
- Patients with a family history of VTE, especially in the presence of transient conditions that increase the risk of thrombosis.
- Relatives of a person diagnosed 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.



7. Patient Data Integration and Online Reporting

Sitab® is a state-of-the art cloud based web portal that provides the health care practitioner with a systemised approach for requesting tests, tracking the process and receiving the clinical and genetic test results in a simple to understand report format.

The bioinformatic tools integrated in Sitab® capture the patients genetic and clinical data and processes this information using algorithms and intelligence to provide a comprehensive risk stratification and a clinically actionable report.



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Thrombo inCode® is available in KIT format for internalisation in analytical laboratories.

Genotyping

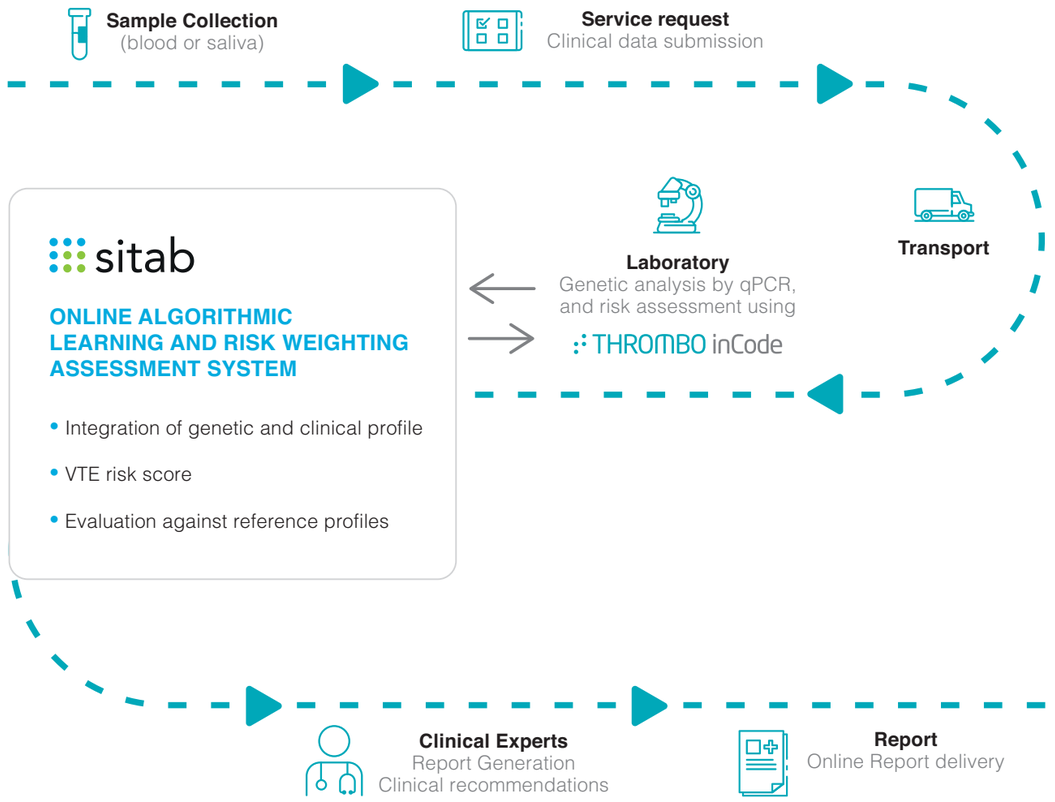
Digitalization thanks to a signature plug-in

Integration into SITAB Platform and algorithmic calculation

Edition of the patient's report

Sitab® allows the health care professional to:

- Request genetic tests easily, quickly and safely
- Manage the shipment of the samples for analysis
- Track and monitor the requested services status
- Review the requested patient reports and full history
- Securely store all patient reports for future reference



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