Intérêt des variants génétiques dans la prédiction du risque de thrombose associée au cancer

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Paris, 22 March 2019
Disclosures

• Consultant or advisory role: Sanofi, Leo Pharma, Pfizer-BMS, Daiichi Sankyo
• Research funding: Sanofi, Leo Pharma
• Speakers’ Bureau: Rovi, Daiichi Sankyo
• Inventor with Dr. José Manuel Soria: GRS VTE & Cancer
Variability of the VTE-Risk
VTE-Risk modifiers
Multiple risk factors

Patient-related factors
- Older age
- Gender
- Race
  - Higher in African Americans
  - Lower in Asians
- Patient comorbidities
- History of VTE

Treatment-related factors
- Major surgery
- Hospitalization
- Chemotherapy
- Central venous catheters
- Hormonal therapy
- Antiangiogenic agents
- ESAs
- Transfusions

Cancer-related factors
- Site of cancer
- Stage
- Initial period after diagnosis

Variability of the VTE-Risk
VTE-Risk modifiers
New Landscape

Patient-related factors
- Older age
- Gender
- Race
  - Higher in African Americans
  - Lower in Asians
- Patient comorbidities
- History of VTE

Treatment-related factors
- Major surgery
- Hospitalization
- Chemotherapy
- Central venous catheters
- Hormonal therapy
- Antiangiogenic agents
- ESAs
- Transfusions

Cancer-related factors
- Site of cancer
- Stage
- Initial period after diagnosis


Patient-related factors
- Genomics

Cancer-related factors
- Genomics
- Other molecular biomarkers
VTE is a multifactorial and complex disease and it’s the final result of a combination of genetic & environmental factors

Multiple genes involved, every gen with variable effect, interacting with the environment

(Soria JM, 2005)
Heritability of thrombosis risk

All the risk assessment models have systematically ignored the genetic base of the VTE in cancer patients (genetic base 60% in general population).

Environmental factors
40%

Genetic risk factors
60%


Age,
Obesity
Tobacco
hypertension
Diabetes
Varicose veins
Congestive cardiac disease
Renal failure
Cancer
Autoimmune diseases
Infections
Hospitalizations
Antipsychotic
Tamoxifen
NSAIDs
Hormone replacement therapy
Pregnancy and puerperium
Strong traumatism
General surgery
Orthopedic surgery
Immobilization
Plastering
Travel >5hours
Modeling VTE risk

Genetic risk factors
- Factor V Leiden G20210A FII 6%
- Def. AT, PC y PS 6%

Environmental factors
- Age
- Obesity
- Tobacco
- Hypertension
- Diabetes
- Varicose veins
- Congestive cardiac disease
- Renal failure
- Cancer
- Autoimmune diseases
- Infections
- Hospitalizations
- Antipsychotic
- Tamoxifen
- NSAIDs
- Hormone replacement therapy
- Pregnancy and puerperium
- Strong traumatism
- General surgery
- Orthopedic surgery
- Immobilization
- Plastering
- Travel >5 hours
Modeling VTE risk

Environmental factors 40%

Factores Genéticos 60%

Environmental factors

Def. AT, PC y PS

Factor V Leiden
G20210A FII
F12
F13
ABO
SerpinC1
SerpinC10

15.1%

Age,
Obesity
Tobacco
hypertension
Diabetes
Varicose veins
Congestive cardiac disease
Renal failure
Cancer
Autoimmune diseases
Infections
Hospitalizations
Antipsychotic
Tamoxifen
NSAIDs
Hormone replacement therapy
Pregnancy and puerperium
Strong traumatism
General surgery
Orthopedic surgery
Immobilization
Plastering
Travel >5hours
Factor V Leiden mutation increases the risk for venous thromboembolism in cancer patients – results from the Vienna Cancer And Thrombosis Study (CATS)

It could be used for individual risk prediction in cancer patients.

Why not to use this info to predict VTE in cancer patients?
Joint effects of cancer and variants in the factor 5 gene on the risk of venous thromboembolism

Olga V. Gran,1 Erin N. Smith,2,3,4 Sigrid K. Brækkan,1,5 Hilde Jensvoll,4,6 Terry Solomon,6 Kristian Hindberg,1 Tom Wilsgaard,7 Frits R. Rosendaal,1,8 Kelly A. Frazer,1,2 and John-Bjarne Hansen1,8

1K.G. Jebsen Thrombosis Research and Expertise Center (TREC), Department of Clinical Medicine, UiT - The Arctic University of Norway, Tromsø, Norway; 2Department of Pediatrics and Rady’s Children’s Hospital, University of California, San Diego, La Jolla, CA, USA; 3Moores Cancer Center, University of California, San Diego, La Jolla, CA, USA; 4Institute for Genomic Medicine, University of California, San Diego, La Jolla, CA, USA; 5Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway; 6Biomedical Sciences Graduate Program, University of California, San Diego, La Jolla, CA, USA; 7Department of Community Medicine, UiT - The Arctic University of Norway, Tromsø, Norway; and 8Department of Clinical Epidemiology, Leiden University Medical Center, the Netherlands

Haematologica 2016
Volume 101(9):1046-1053

active cancer. A synergistic interaction was observed between active cancer and factor V Leiden (relative excess risk due to interaction 7.0; 95% CI 0.5-14.4) and rs4524 (relative excess risk due to interaction 15.0; 95% CI 7.5-29.2). The incidence of venous thromboembolism during the initial 6 months following a diagnosis of cancer was particularly high in subjects with risk alleles at these loci. This implies that the combination of cancer and F5 variants synergistically increases venous thromboembolism risk.
Modeling the risk of VTE

Abstract

Purpose: Venous thromboembolism (VTE) is highly heritable and a serious complication of cancer and its treatment. We examined the individual and joint effects of chemotherapy and genetic susceptibility on VTE risk in patients with breast cancer.

Experimental Design: A Swedish population-based study including 4,261 women diagnosed with primary invasive breast cancer between 2001 and 2008 in Stockholm, followed until 2012. Risk stratification by chemotherapy and genetic susceptibility [a polygenic risk score (PRS), including nine established VTE loci] was assessed using Kaplan–Meier and flexible parametric survival analyses, adjusting for patient, tumor, and treatment characteristics.

Results: In total, 276 patients experienced a VTE event during a median follow-up of 7.6 years. Patients receiving chemotherapy [HR (95% CI) = 1.98; 1.40–2.80] and patients in the highest 5% of the PRS [HR (95% CI) = 1.90; 1.24–2.91] were at increased risk of developing VTE. Chemotherapy and PRS acted independently on VTE risk and the 1-year cumulative incidence in patients carrying both risk factors was 9.5% compared with 1.3% in patients not having these risk factors (P < 0.001). Stratified analyses by age showed that the risk-increasing effect of PRS was stronger in older patients (P interaction = 0.04), resulting in an excess risk among genetically susceptible patients receiving chemotherapy aged ≥ 60 years (1-year cumulative incidence = 25.0%).

Conclusions: Risk stratification by chemotherapy and genetic susceptibility identifies patients with breast cancer at high VTE risk, who could potentially benefit from thromboprophylaxis. Our results further suggest that genetic testing is more informative in older patients with breast cancer. Clin Cancer Res 22(21): 5249–55. ©2016 AACR.
## Modeling the risk of VTE

**Dr. Soria/H. Sant Pau genetic risk score**

<table>
<thead>
<tr>
<th>SNPs</th>
<th>Gene</th>
<th>Prevalence in DVT patients</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>46C&gt;T</td>
<td>FXII</td>
<td>6%</td>
<td>5</td>
</tr>
<tr>
<td>rs8176719</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs7853989</td>
<td>ABO Group (A1 carriers)</td>
<td>nd</td>
<td>2-4 (+ FV Leiden: 4-23)</td>
</tr>
<tr>
<td>rs8176743</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs8176750</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arg67Stop</td>
<td>Serpin A10</td>
<td>4,4 %</td>
<td>3,3</td>
</tr>
<tr>
<td>Ala384Ser</td>
<td>Serpin C1</td>
<td>1,7 %</td>
<td>10</td>
</tr>
<tr>
<td>(Cambridge II)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arg506Gln</td>
<td>Factor V (FV)</td>
<td>15-25%</td>
<td>5</td>
</tr>
<tr>
<td>(FV Leiden)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arg306Thr</td>
<td></td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>(FV Cambridge)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arg306Gly</td>
<td></td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>(FV Hong Kong)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val34Leu</td>
<td>Factor XIII (FXIII)</td>
<td>2%</td>
<td>Protective factor</td>
</tr>
<tr>
<td>G20210A</td>
<td>Prothrombin Factor II (FII)</td>
<td>6-16%</td>
<td>2-3</td>
</tr>
</tbody>
</table>

12 SNPs in 7 genes
Genomic factors included in TiC
Multilocus Genetic Risk Scores for Venous Thromboembolism Risk Assessment

José Manuel Soria, BSc, PhD; Pierre-Emmanuel Morange, MD, PhD; Joan Vila, PhD; Juan Carlos Souto, MD, PhD; Manel Moyano, BSc; David-Alexandre Trégouët, BSc, PhD; José Mateo, MD, PhD; Noémi Saut, BSc, PhD; Eduardo Salas, MD, PhD; Roberto Bosua, MD, PhD

Background—Genetics plays an important role in venous thromboembolism (VTE). Factor V Leiden (FVL or rs6025) and prothrombin gene G20210A (PT or rs1799963) are the genetic variants currently tested for VTE risk assessment. We hypothesized that primary VTE risk assessment can be improved by using genetic risk scores with more genetic markers than just FVL-rs6025 and prothrombin gene PT-rs1799963. To this end, we have designed a new genetic risk score called ThromboinCode (TiC).

Methods and Results—TiC was evaluated in terms of discrimination (A of the area under the receiver operating characteristic curve) and reclassification (integrated discrimination improvement and net reclassification improvement). This evaluation was performed using 2 age- and sex-matched case-control populations: SANTPAU (248 cases, 249 controls) and the Marseille Thrombosis Association study (MARTHA; 477 cases, 477 controls). TiC was compared with other literature-based genetic risk scores. TiC including F5 rs6025/rs118203906/rs118203905, F2 rs1799963, F12 rs1801020, F13 rs5985, SERPINC1 rs121909548, and SERPINA10 rs2232698 plus the A1 blood group (rs8176719, rs7853989, rs8176743, rs8176750) improved the area under the curve compared with a model based only on F5-rs6025 and F2-rs1799963 in SANTPAU (0.677 versus 0.575, P=0.001) and MARTHA (0.605 versus 0.576, P=0.008). TiC showed good integrated discrimination improvement of 5.49 (P=0.001) for SANTPAU and 0.96 (P=0.045) for MARTHA. Among the genetic risk scores evaluated, the proportion of VTE risk variance explained by TiC was the highest.

Conclusions—We conclude that TiC greatly improves prediction of VTE risk compared with other genetic risk scores. TiC should improve prevention, diagnosis, and treatment of VTE. (J Am Heart Assoc. 2014;3:e001060 doi: 10.1161/JAHA.114.001060)
Results

PE study: Dr. Soria validation at Sant Pau Hospital
- Retrospective case and control study in a Spanish population
- 249 cases/248 controls (cases: 111 males, 138 females; 47.1+14.0 years old; & 248 controls; 109 males, 139 females; 49.0+14.9 years old).

MARTHA study: Dr. Morange validation at Marseille
- Retrospective case and control study in a French population.
- Enriched study with FV Leiden and FII G20210A to evaluate the association of FV Leiden and the FII mutation with other risk factors.
- 1150 cases/801 controls (cases: 347 males, 803 females; 38.0+13.9 years old; & controls: 383 males, 418 females; 47.4+14.0 years old).

Statistical Analyses:
Predictive Capacity (estadisgraph c; AUC: area under the curve). All variants vs FVL-F2.

Reclassification (NRI: net reclassification improvement, IDI: integrated discrimination improvement), all variants vs FVL-F2
## Case-control study Sant Pau & France

<table>
<thead>
<tr>
<th>Genetic Factor</th>
<th>Models</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>FVL</td>
<td>X</td>
</tr>
<tr>
<td>G20210A</td>
<td>X</td>
</tr>
<tr>
<td>ABO</td>
<td>X</td>
</tr>
<tr>
<td>C46T F12</td>
<td>X</td>
</tr>
<tr>
<td>V34L F13</td>
<td>X</td>
</tr>
<tr>
<td>A384S SerpinC1</td>
<td>X</td>
</tr>
<tr>
<td>R67X SerpinA10</td>
<td>X</td>
</tr>
<tr>
<td>FGG</td>
<td></td>
</tr>
<tr>
<td>F11</td>
<td></td>
</tr>
</tbody>
</table>

| AUC            | 0.57   | 0.69   | 0.64   | 0.68   |

Better predictive model

1. FVL+PT
2. Soria et al JAHA 2014
3. De Haan et al Blood 2012
4. Soria et al + De Haan et al
Clinical (translational) applicability:
FLV-PT vs Genetic Profile in specific clinical circumstances
MIRTO PROGRAM: Oncothromb Project

Dr. Andrés Muñoz. Oncología Médica. Hospital Gregorio Marañón. Madrid
Dr. Juan Carlos Souto. Hematología. Hospital de Sant Pau (IIB-Sant Pau). Barcelona
Dr. José Manuel Soria. UGMC. Hospital de Sant Pau (IIB-Sant Pau). Barcelona

Cancer_Thrombosis Working Group. Spanish Society of Clinical Oncology (SEOM)

Dra. Julia Calzas. Hospital Universitario de Fuenlabrada
Dra. Carme Font. Hospital Clínic. Barcelona
Dra. Victoria Eugenia Castellón. Hospital Torrecárdenas. Almería
Dra. Eva María Martínez de Castro. Hospital Marques de Valdecilla. Santander
• ONCOTHROMB is a prospective, translational, observational, cohort study

• 406 patients diagnosed with colorectal, esophago-gastric, pancreas and lung cancer receiving systemic outpatient chemotherapy were included from eight centers of Cancer & Thrombosis Working Group, Spanish Society of Medical Oncology (SEOM)

• Patients were followed-up for 18 months

• We hypothesized that using a combination of a genetic risk score (GRS) and clinical parameters can improve VTE prediction compares to Khorana score
Clinical Characteristics
ONCOTHROMB12-01

<table>
<thead>
<tr>
<th>Table 2. Population characteristics per cancer type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour type</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Patients (%)</td>
</tr>
<tr>
<td>No-VTE</td>
</tr>
<tr>
<td>VTE</td>
</tr>
<tr>
<td>% VTE</td>
</tr>
<tr>
<td>Stage I + II</td>
</tr>
<tr>
<td>Stage III</td>
</tr>
<tr>
<td>Stage IV</td>
</tr>
<tr>
<td>Death, n (%)</td>
</tr>
<tr>
<td>VTE death, n (%)</td>
</tr>
<tr>
<td>No-VTE deaths, n (%)</td>
</tr>
</tbody>
</table>
Khorana score doesn’t work
ONCOTHROMB12-01

<table>
<thead>
<tr>
<th>Khorana</th>
<th>VTE</th>
<th>No-VTE</th>
<th>Patients (n)</th>
<th>Patients (%)</th>
<th>% VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14</td>
<td>94</td>
<td>108</td>
<td>27.62</td>
<td>12.96</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>74</td>
<td>85</td>
<td>21.74</td>
<td>12.94</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>92</td>
<td>122</td>
<td>31.20</td>
<td>24.59</td>
</tr>
<tr>
<td>≥3</td>
<td>16</td>
<td>58</td>
<td>74</td>
<td>18.93</td>
<td>21.62</td>
</tr>
<tr>
<td>NA</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0.51</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>320</td>
<td>391</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients (%) percentage of patients per Khorana score level. %VTE cases percentage of patients with VTE in relation to the number of patients per Khorana score level
The most important variables related to VTE:

• Type of tumor
• Stage of the disease
• GRS
### Table 4. Predictive capability of TiC-Onco and Khorana scores

<table>
<thead>
<tr>
<th></th>
<th>TiC-Onco (1)</th>
<th>TiC-Onco (2)</th>
<th>Khorana</th>
<th>p (TiC-Onco (1) vs Khorana)</th>
<th>p (TiC-Onco (2) vs Khorana)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (95% CI)</td>
<td>0.734 (0.67–0.79)</td>
<td>0.734 (0.67–0.79)</td>
<td>0.580 (0.51–0.65)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sensitivity, % (95% CI)</td>
<td>49.30 (37.7–60.9)</td>
<td>85.92 (77.8–94.0)</td>
<td>22.54 (12.8–32.3)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Specificity, % (95% CI)</td>
<td>81.25 (77.0–85.5)</td>
<td>49.06 (43.6–54.5)</td>
<td>81.76 (77.5–86.0)</td>
<td>0.823</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PPV, % (95% CI)</td>
<td><strong>36.84 (27.1–46.5)</strong></td>
<td>27.23 (21.4–33.1)</td>
<td>21.62 (12.2–31.0)</td>
<td>0.004</td>
<td>0.218</td>
</tr>
<tr>
<td>NPV, % (95% CI)</td>
<td>87.84 (84.1–91.6)</td>
<td>94.01 (90.4–97.6)</td>
<td>82.54 (78.3–86.7)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PLR (95% CI)</td>
<td>2.63 (1.89–3.65)</td>
<td>1.69 (1.46–1.95)</td>
<td>1.24 (0.76–2.02)</td>
<td>0.005</td>
<td>0.244</td>
</tr>
<tr>
<td>NLR (95% CI)</td>
<td>0.62 (0.49–0.79)</td>
<td>0.29 (0.16–0.52)</td>
<td>0.95 (0.83–1.09)</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TiC-Onco (1) shows the predictive capabilities for the default cut-off (see Methods). TiC-Onco (2) shows the predictive capabilities for the cut-off providing the best Youden’s Index. AUC Area Under the Roc Curve, PPV Positive Predictive Value, NPV Negative Predictive Value, PLR Positive Likelihood Ratio, NLR Negative Likelihood Ratio.

### Table 5. Percentage of study population among risk categories, and percentage of patients with VTE. See Methods for details about the definition of two and three categories.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>% of cancer population</th>
<th>% of cancer patient with VTE</th>
<th>Khorana</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% of cancer population</td>
</tr>
<tr>
<td>High risk</td>
<td>24.30</td>
<td>36.84</td>
<td>18.93</td>
</tr>
<tr>
<td>Non-high risk</td>
<td>75.70</td>
<td>12.16</td>
<td>—</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>30.13</td>
<td>18.30</td>
<td>52.94</td>
</tr>
<tr>
<td>Low risk</td>
<td>36.57</td>
<td>55.9</td>
<td>27.62</td>
</tr>
</tbody>
</table>

### Risk assessment models for specific neoplasms

**Throly score**

The Thro(MBOSIS) Ly(MPHOMA) score uses the following variables and points:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE</td>
<td>2</td>
</tr>
<tr>
<td>Reduced mobility</td>
<td>1</td>
</tr>
<tr>
<td>Previous AMI/stroke</td>
<td>2</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 25)</td>
<td>2</td>
</tr>
<tr>
<td>Extranodal</td>
<td>1</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
</tr>
<tr>
<td>Hb &lt; 100</td>
<td>1</td>
</tr>
</tbody>
</table>

- **Low risk** – 0–1
- **Intermediate risk** – 2–3
- **High risk** – ≥ 4

Antic et al. Presented @ ICTHIC congress 2018 (Bergamo, Italy)
Score Validation in Lymphoma

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Dr. José Manuel Soria. UGMC. Hospital de Sant Pau (IIB-Sant Pau). Barcelona

Observational retrospective unicentric study Hospital General Universitario Gregorio Marañón, Madrid, Spain

<table>
<thead>
<tr>
<th>Score</th>
<th>Sensivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tic Linfo</td>
<td>90.32</td>
<td>58.43</td>
</tr>
<tr>
<td>Khorana</td>
<td>35.48</td>
<td>71.79</td>
</tr>
<tr>
<td>Throly</td>
<td>45.16</td>
<td>64.74</td>
</tr>
</tbody>
</table>

208 patients with Lymphoma
31 VTE+ vs 177 VTE-

<table>
<thead>
<tr>
<th>Score</th>
<th>AUC</th>
<th>(95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ThroLy</td>
<td>0.569</td>
<td>(0.495-0.641)</td>
<td>0.2066</td>
</tr>
<tr>
<td>Khorana</td>
<td>0.53</td>
<td>(0.455-0.603)</td>
<td>0.641</td>
</tr>
<tr>
<td>TiC-Linfo</td>
<td>0.765</td>
<td>(0.702-0.821)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Spanish Society of Thrombosis and Haemostasis Congress 2018

Pascual C et al. SETH Congress 2018

ISTH Submitted
Unpublished data
(manuscript in preparation)
Score Validation Program 2019

• Retrospective validation in Vienna CAT cohort

• Prospective validation adding D-dimer (multicentre study):
  – Cancer & Thrombosis Working Group SEOM (Spain)

• Validation in a single cancer:
  – NSCLC

• Pilot study adding circulating tumor cells (CTCs) in pancreatic cancer
Next steps

• Add treatment variables to TiC score
  – For example, cisplatin-carboplatin-gemcitabine or megestrol acetate (related to VTE risk)

• Add other biomarkers:
  – miRNA, NETs, TF, etc.

• The genomic of the neoplasm!

1992 Bill Clinton election
This is the economy (stupid)!

2019 THIS IS CANCER!
Next steps
Include genomics of the neoplasm

Differential gene expression in lung cancer patients with and without VTE

Genes over-expressed in patients with VTE

Genes under-expressed in patients with VTE

Sussman et al. Blood 2017; 130:554
NSCLC ALK+ and VTE

- Zugazagoitia, Muñoz & Manzano et al. European Respiratory Journal 2018
  - 241 ALK-rearranged NSCLC patients
  - 73 patients (30 %) developed thromboembolic disease
  - 74% in the first 6 months from cancer diagnosis
  - 16% recurrent VTE
    - Liver mets: significant risk factor
    - mOS VTE+ 20 months vs VTE- 36 months (p=0.036)
    - mOS VTE at baseline 15 m
    - mOS recurrent VTE 10 m

- Toronto IASCL 2018: METROS trial ROS1-rearranged NSCLC VTE+ 42%
Podoplanin was associated with a high risk of VTE

While mutant IDH-1-R12H was associated with a very low risk for VTE

IDH-1-R132H mutation is only detected in tumors, which are podoplanin negative

– Subhazard ratio (SHR) for podoplanin positive plus IDH-1-R132H wt tumors, compared to podoplanin negative plus IDH-1-R132H mutant tumors: 4.69, 95%CI: 1.28-17.17; p=0.020.

**PROTECTIVE FACTOR!**

**IDH mutation**

**FIGURE 1** (A) IDH-1 R132H mutation according to podoplanin expression. (B) Incidence of VTE according to podoplanin expression and IDH-1 R132H mutation
Conclusions

• Genetic testing could help identify cancer patients who are at high risk of experiencing VTE

• The inclusion of genomic profiles, not only FVL and PT mutations, in risk assessment models significantly improves prediction of VTE risk compared with Khorana score (in solid cancer patients) and ThroLy score (in lymphoma patients)

• The risk assessment model that include genetic and clinical variables are the models with the higher capacity of prediction of VTE
Conclusions

• The results of this project have a direct applicability that will eventually may change clinical practice and therefore be the first approach to personalized medicine in this setting
Acknowledgments

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