ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

Cancer-associated thrombosis or ***CAT***
Epidemiology, pathophysiology, needs

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Outline

1. Epidemiological data
2. Risk factors / Risk assessment
3. Pathophysiology
4. Needs

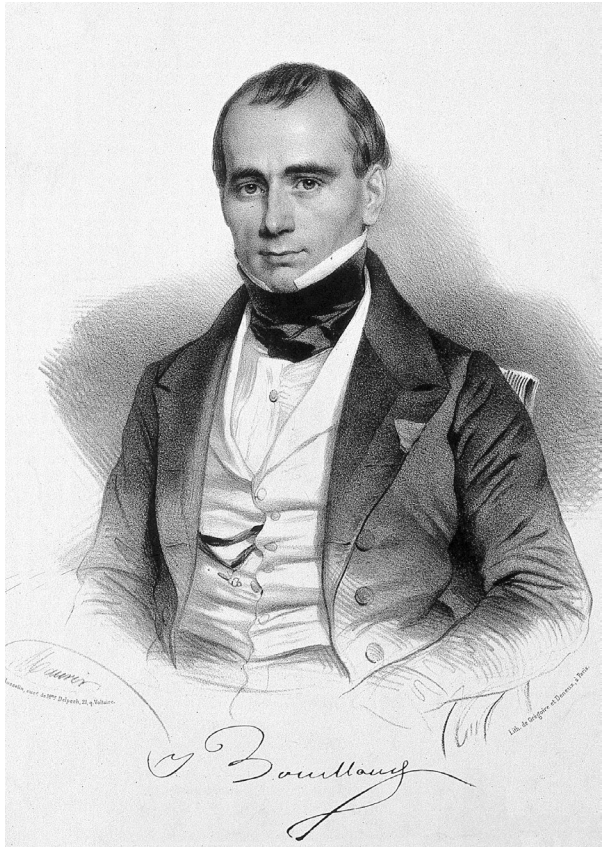
Epidemiological data

- Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, or nearly one in six deaths
- About 4 - 20% of patients with cancer experience venous thrombosis

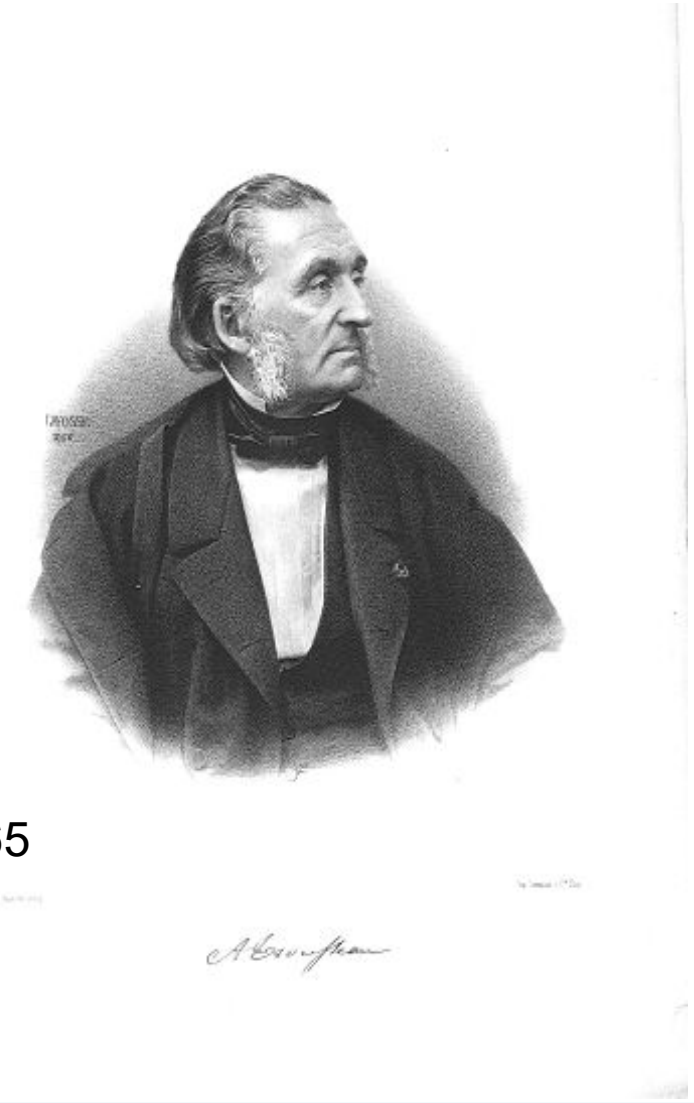
Khorana AA et al. *J Thromb Haemost*. 2007;5(3):632-634.

First reports on association between cancer and thrombosis

1823



1865



Bouillard JB, Bouillaud S. *Arch Gen Med*. 1823;1:188-204; Trousseau A. *Clinique Medicale de l'Hotel-Dieu de Paris, 2nd edition*. 1865;3:654-712

CAT

- Includes mainly venous thromboembolism (VTE): deep vein thrombosis (DVT), pulmonary embolism (PE), recurrent migratory thrombophlebitis
- Common complication in patients with cancer
  - Annual VTE incidence in general population: 1 to 2 per 1000
  - In cancer patients: 4 to 7 times higher
- VTE in cancer patients leads to higher morbidity, mortality and economic burden compared to those without VTE
- 2nd leading cause of death in cancer patients
- In nearly 20% of all newly diagnosed unexplained VTE cases, cancer is diagnosed within the next 3 to 6 months

Walker AJ et al. *Eur J Cancer*. 2013;49(6):1404-1413; Cohen AT et al. *Thromb Haemost*. 2017;117(1):57-65; Khorana AA et al. *J Thromb Haemost*. 2007;5(3):632-634.

Risk factors for CAT

Patient-related

- Medical comorbidities (CCI ≥3)
- Presence of varicose veins
- Prior VTE
- Hereditary risk factors (e.g., factor V Leiden)

Tumour-related

- Site of cancer
  - Very high: stomach, pancreas
  - High: lung, hematologic, gynecologic, brain, renal, bladder
- Histological grade of a tumour
- Stage of cancer/metastases
- Time since cancer diagnosis

Treatment-related

- Platinum-based and other chemotherapy
- Anti-angiogenesis agents
- Hormonal therapy
- Surgery
- Radiotherapy
- Blood transfusion
- Central venous catheters
- Immobility and hospitalization

Biomarkers

- Hematologic biomarkers (e.g., platelet, haemoglobin, leukocyte counts)
- D-dimer
- P-selectin
- Prothrombin fragment 1 + 2
- Thrombin generation potential
- Microvesicle-tissue factor activity
- C-reactive protein

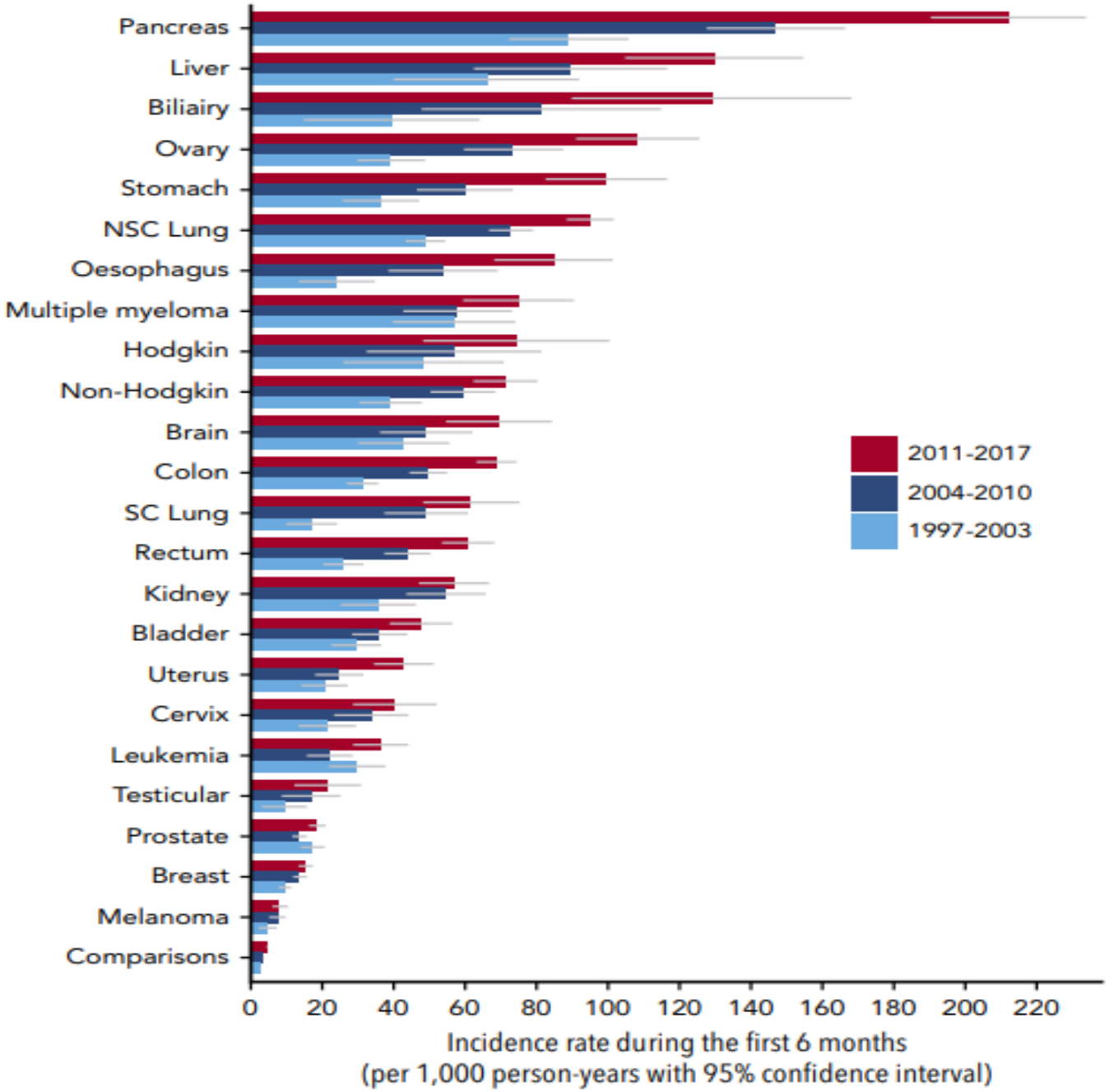
CCI, Charlson Comorbidity Index

Adapted from Ay C et al. *Thromb Haemost*. 2017;117(2):219-230.

CAT incidence

Incidence rate of VTE during the first 6 months after cancer diagnosis by cancer type for 3 calendar-year periods

Increasing in time



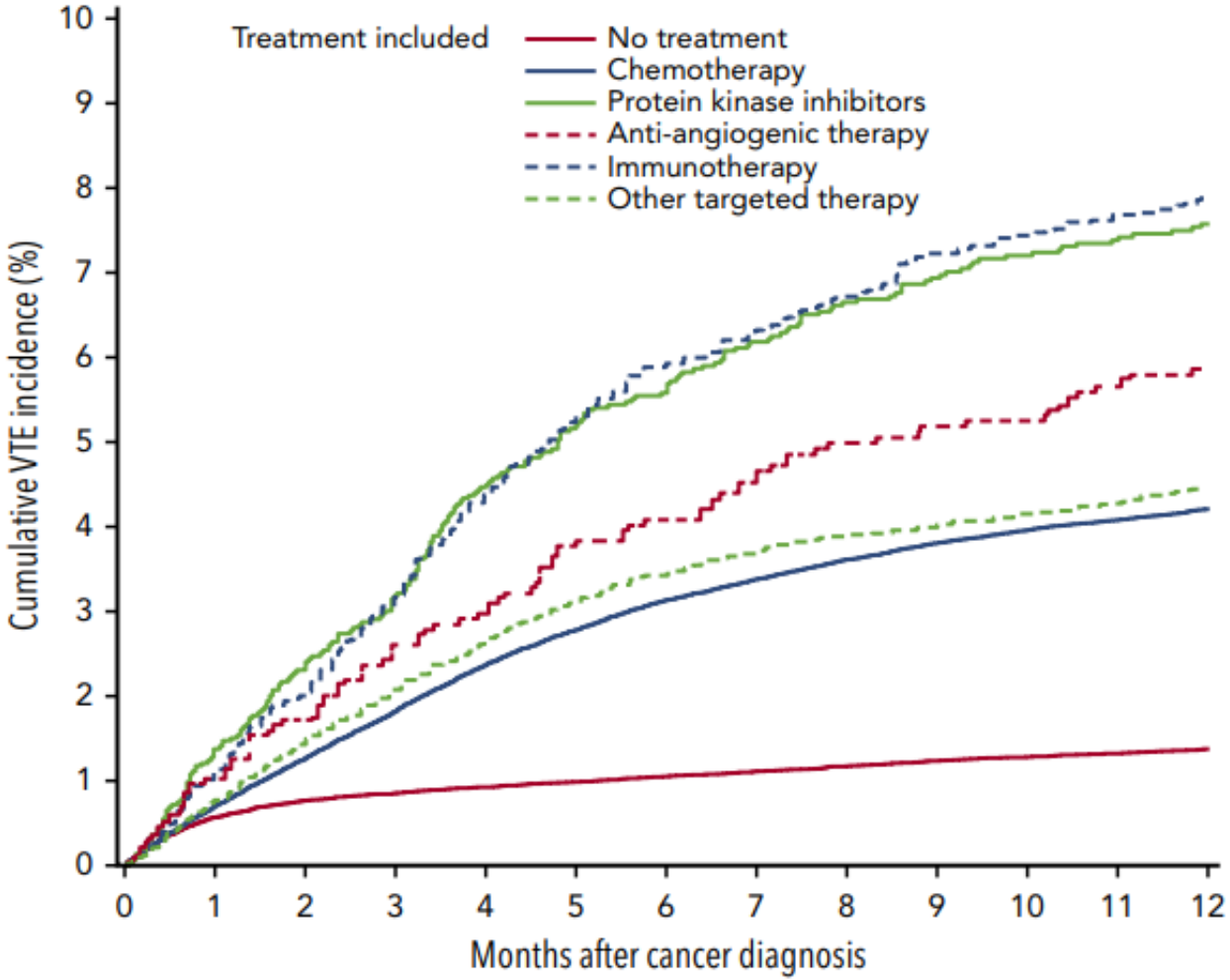
Mulder FI et al. Blood 2021; 137:1959-69

CAT incidence

- Increasing in time
- Potential contributing factors:
  - Increased survival
  - Increased use of CT scans (incidental PE findings)
  - Increased use of chemotherapy and targeted therapy

Mulder FI et al. *Blood*. 2021;137(14):1959-1969.

CAT incidence



12-month cumulative incidence of VTE in cancer patients receiving systemic therapy during the first 4 months after cancer diagnosis

Reproduced from Mulder FI et al. *Blood*. 2021;137(14):1959-1969.

Risk assessment models

- Goal: identify patients at high risk for CAT with eventual benefit of primary thromboprophylaxis

- Several models available with advantages/drawbacks
  - *Khorana score*: includes cancer site, platelet/leucocyte count, haemoglobin level or EPO use, BMI
  - *Vienna CATS score*: adding sP-selectin and D-dimer levels

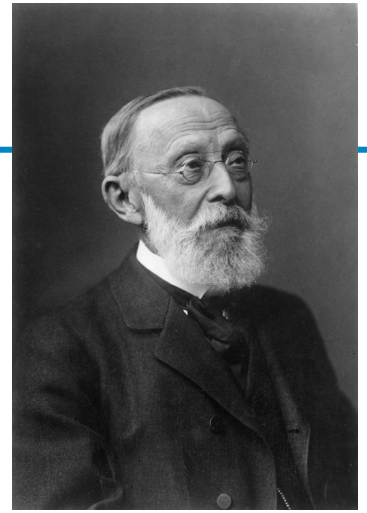
  Scores with good negative predictive value if low (98,5% and 99,0%, resp.), but rather poor positive predictive values if high (7,1% and 42,9%, resp.)

Khorana AA et al. *Blood*. 2008;111(10):4902-4907; Ay C et al. Blood. 2010;116(24):5377-5382.

Pathophysiology of CAT

Multifactorial and involving multiple overlapping pathways

Virchow's triad → *blood flow*, *vessel wall*, *blood components*



1856

Pathophysiology of CAT

- Venous stasis (increased immobility)
- Vessel wall injury/endothelial damage

  (tumour invasion, secreted vascular permeability factors, chemotherapy, surgery, catheters, …)

Kyrle PA et al. *Blood*. 2009;114(6):1138-1139.

Pathophysiology of CAT

- Hypercoagulability / interaction with host blood cells
  - Upregulation of pro-coagulant factors (like tissue factor)
  - Shedding of pro-coagulant microvesicles from cancer cells, blood cells and endothelial cells
  - Downregulation of anticoagulant factors (inhibition of fibrinolysis)
  - Release of pro-inflammatory cytokines (like interleukin-6)
  - Formation of neutrophil extracellular traps (DNA fibers promoting platelet activation and fibrin deposition)

Ay C et al. *Thromb Haemost*. 2017;117(2):219-230; Falanga A et al. *Crit Rev Oncol Hematol*. 2017;118:79-83; Fuchs TA et al. *Proc Natl Acad Sci USA*. 2010;107(36):15880-15885.

Pathophysiology of CAT

Role of cancer-specific somatic genetic alterations

- Molecular studies demonstrate that oncogenes responsible for the cellular neoplastic transformation drive the programs of hemostatic protein expression and microparticle liberation by cancer tissues
- Activated coagulation may possess cancer-specific properties

Falanga A et al. *Cancer Treat Res*. 2019;179:11-36; Mantha S et al. *Thrombosis Research* 2022;213:S29-34; Magnus N et al. *Thromb Res* 2014:133(Suppl 2):S1–S9.

Pathophysiology of CAT

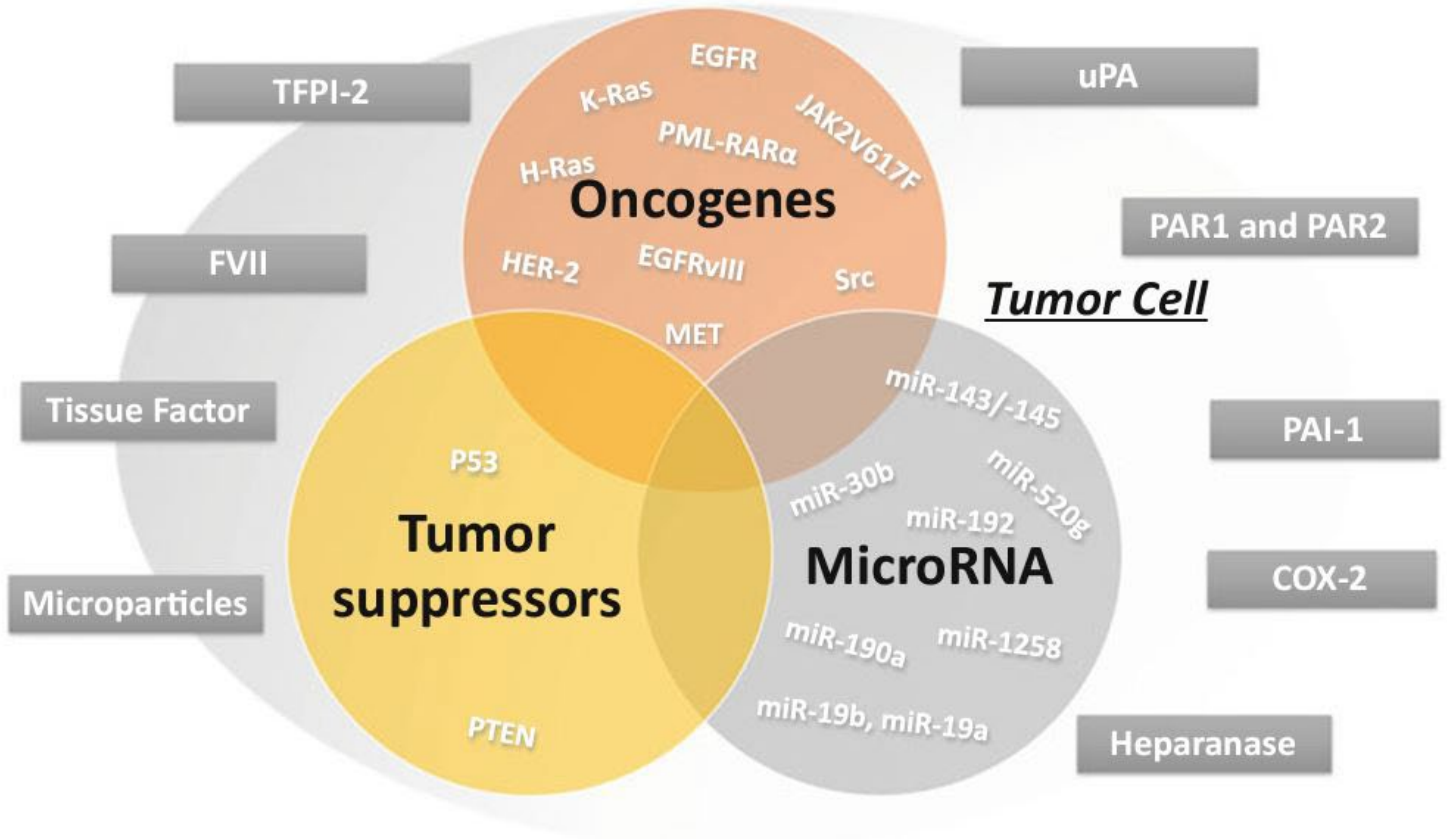
Role of cancer-specific somatic genetic alterations

- Molecularly different subtypes of cancer exhibit different coagulation patterns or '*coagulomes*', i.e., the expression of multiple genes and proteins, across different primary tumor types, contributing to the equilibrium between coagulation and fibrinolysis
- CAVE the complexity with 100s of oncogenes/tumor suppressor genes and about 100 coagulation-related genes. And those genes can be altered in multiple ways…

Falanga A et al. *Cancer Treat Res*. 2019;179:11-36; Mantha S et al. *Thrombosis Research* 2022;213:S29-34; Magnus N et al. *Thromb Res* 2014:133(Suppl 2):S1–S9.

Pathophysiology of CAT

- Oncogenes, tumor suppressor genes, and microRNA implicated in hypercoagulability in cancer
- Genes for neoplastic transformation also drive the programs for the expression of hemostatic proteins in cancer tissues



Falanga A et al. *Cancer Treat Res*. 2019;179:11-36; Mantha S et al. *Thrombosis Research* 2022;213:S29-34.

Some needs

- Patient education on VTE signs and symptoms
- More accurate and easier-to-apply biomarkers and risk stratification models
- Study of ‘tumor coagulome’ via tumor (liquid?) biopsies, possibly serving as prognostic biomarker in certain cancer types
- Cancer type-specific studies (but by the time results are known other treatments are already available… ‘following the facts…’)
- …