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Dynamic thromboembolism risk modelling in patients with cancer: prospective study

BIOmarkers for risk of ThromboEmbolism in patients with Lung cancer (BIOTEL)

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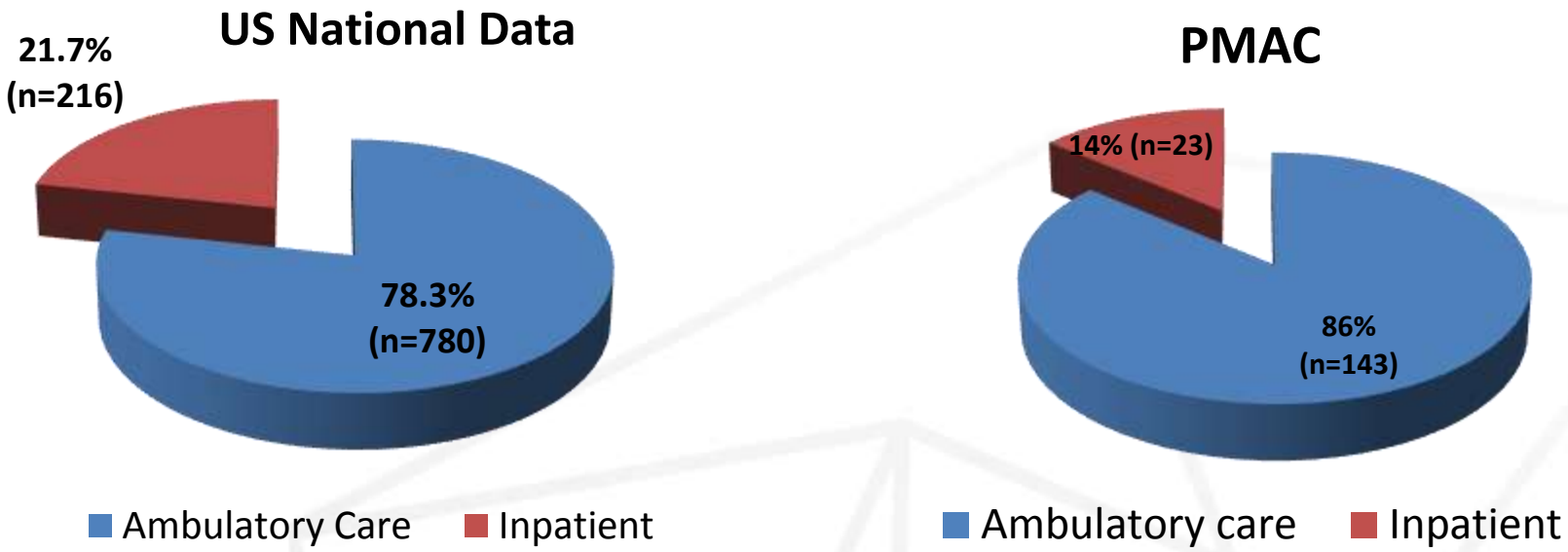
Cancer associated thromboembolism (CA-TE): remains a priority area

- **Important and frequent complication:** substantial adverse clinical and economical consequences
  - Represents major clinical event for patients with cancer
  - Preventable
- 80% CA-TE occur in ambulatory care settings
- **Heterogeneity of TE risk** (patients, tumour type and treatments)
- **Coagulation and tumour biology**

PRIOIRTY AIMS

- Identification high TE risk patients and time periods
- Simple, relevant real time decision-making algorithm for prevention CA-TE
- Can primary thromboprophylaxis also impact tumour biology

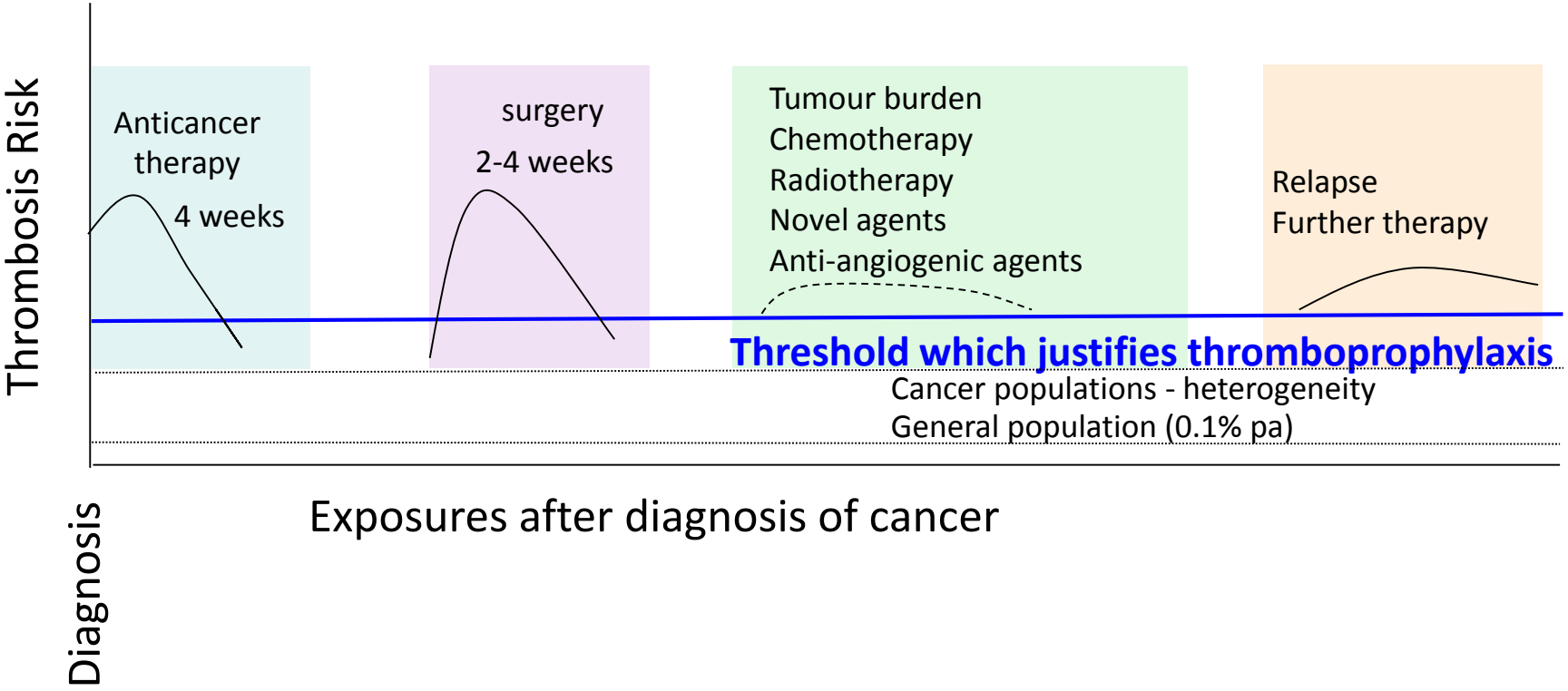
TE: ambulatory vs hospitalised cancer patients



Khorana AA, *Cancer* 2013
Burbury K et al. Lung Cancer. 2016
Burbury et al. Leuk Lymph 2014

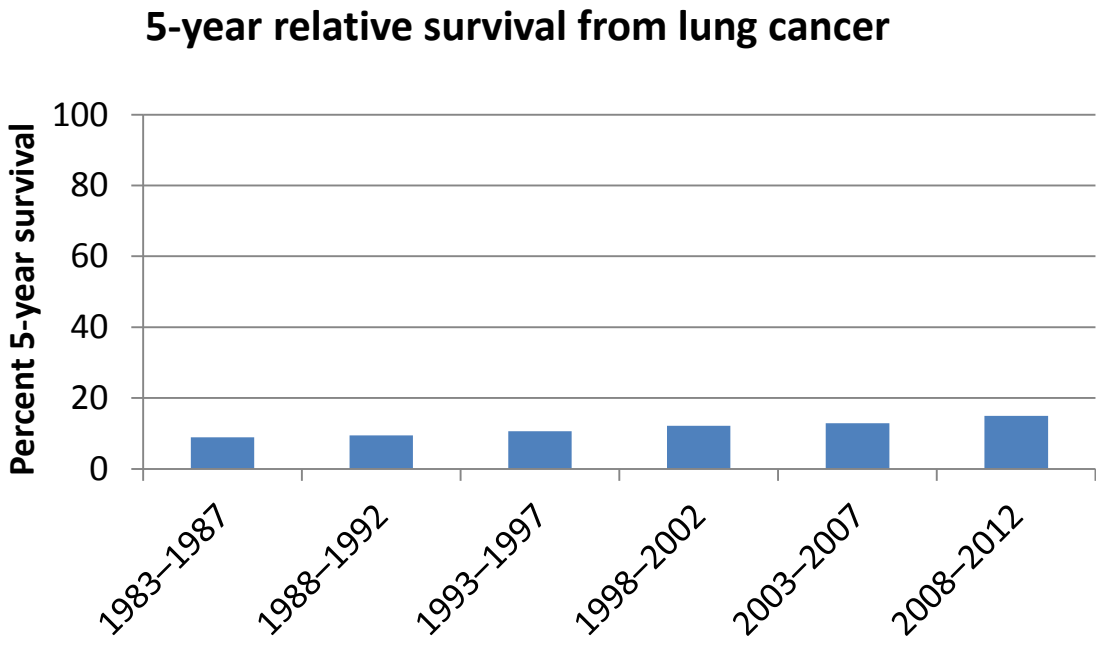
Cancer-associated TE risk: heterogeneous and dynamic

- Inter- and intra-patient variability



Prospective studies: profile risk

- Multiple myeloma
- Post liver resection for cancer
- GI cancer: BIOTEGIC
- **Lung cancer: BIOTEL**



BIOTEL: BIOmarkers for risk of ThromboEmbolism in patients with Lung cancer

Thromboembolism Risk Modelling in Patients with Non-Small Cell Lung Cancer: A Prospective Cohort Study

Burbury *et al*. 2018, under review

Prospective, longitudinal profile of patients with NSCLC receiving anticancer therapy:

- Investigate clinical + lab biomarkers – TE +complications, PFS, OS
- Identify high risk patients and time periods
- Development: TE risk assessment model with decision-making algorithm.

BIOTEL

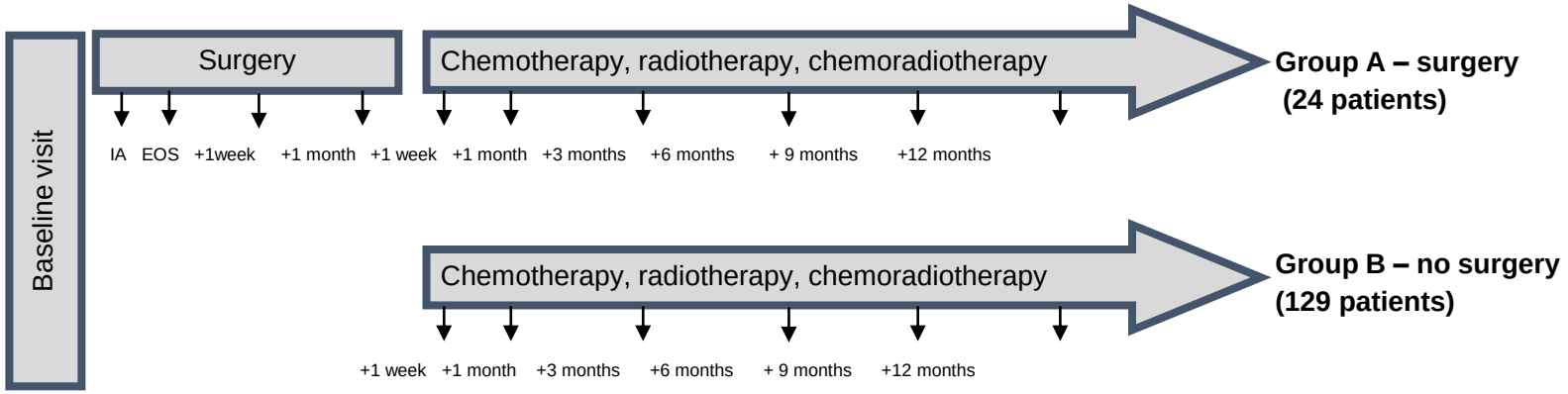
Methods: Study schema

Biomarker panel: clinical and biomarkers

1. Identify eligible NSCLC patients referred for therapy and obtain consent to enter on study

2. Obtain baseline information (demographic, clinical and laboratory assessments)

3. Perform longitudinal clinical assessments and biomarker assays (as outlined below)



Anticancer Therapy → **Sequential Biomarker Profiling** → **TE/PFS/OS**

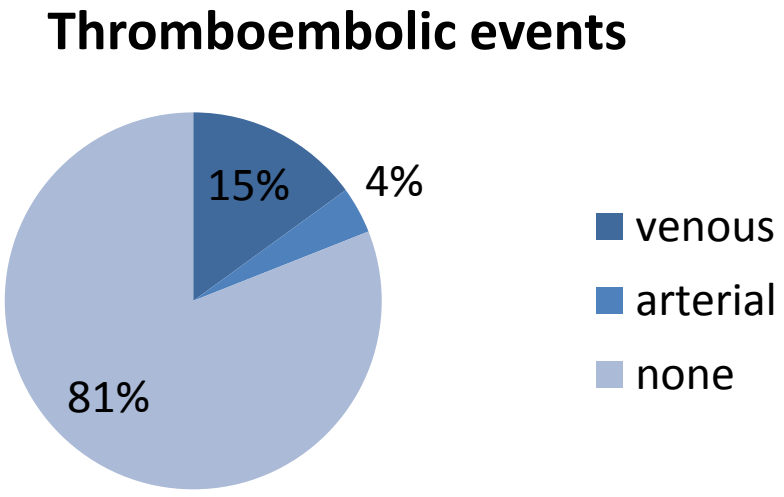
BIOTEL: Laboratory biomarker panel

- FBC
  - Haemoglobin
  - White cell count
  - Platelet count
  - PLR
  - NLR
- Thromboelastography
- Coagulation parameters
  - APTT, PT
  - D-dimer
  - fibrinogen
- Neutrophil-lymphocyte ratio (NLR)
- Platelet-lymphocyte rato (PLR)
- FVIIIc
- vWF-Ag
- Thrombin-antithrombin (TAT)
- Prothrombin fragment (PF1+2)
- Fibrin Monomers (FM)
- Thrombomodulin
- PPL- microparticles
- ETP

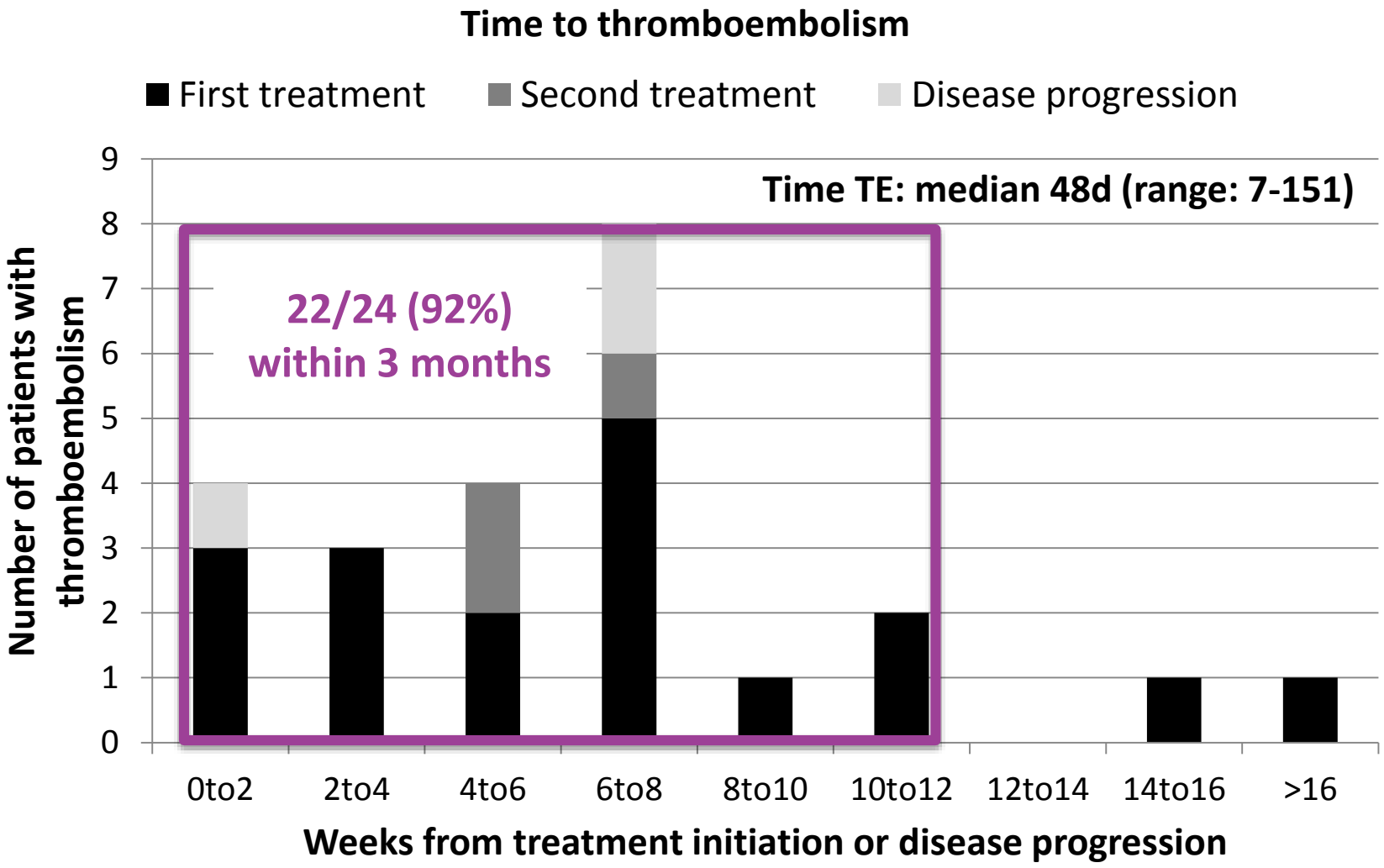
- Thresholds: continuous and binary (reference ranges, pre-defined prediction, informed by data)
- Risk models: derived Fine and Gray proportional hazards regression (death a competing risk).
- Risk prediction models: compared to established models using Bayesian Information Criterion (BIC), C-index, and sensitivity and specificity.
- The model further validated within a prospective gastrointestinal cancer cohort.

BIOTEL

- **Results – non-surgical cohort (n=129)**
  - Median follow-up 22 months (range 5.9-31.3 months)
  - 610 blood samples from 129 patients analysed [median 5 time points/patient (range 1-9)]
  - **24/129 (19%) patients: TE event**
  - **24/170 (14%)** excluded due to TE event at/during screening



BIOTEL: time to thromboembolic event



Risk Factors for TE (Clinical)

Risk factor	All (n=129)			Chemotherapy (n=93)		
	sHR[a]	95%CI	P	sHR[a]	95%CI	P
Chemo (CRT/CHT) vs. RT	6.7	0.8-53.3	0.07	Not applicable		
Stage IV (vs. I-III)	1.1	0.3-4.2	0.83	1.1	0.3-4.2	0.85
Stage IIIB/IV (vs. I-IIIA)	1.7	0.6-5.0	0.30	1.2	0.4-3.5	0.71
New (vs. recurrent)	2.4	0.5-10.2	0.25	1.5	0.3-6.3	0.25
Adenocarcinoma (vs. other)	1.3	0.5-3.2	0.62	1.3	0.5-3.8	0.58
Age ≥70 years	2.6	1.0-7.0	0.06	0.4	0.2-1.2	0.11
Female sex	1.5	0.6-3.8	0.43	1.4	0.5-4.0	0.49
BMI>30kg/m2[a]	0.7	0.2-3.2	0.66	0.5	0.1-4.2	0.52
ECOG PS ≥2	5.9	0.8-41.9	0.08	8.6	1.2-63.0	0.03
Ever smoker	2.0	0.3-15.9	0.50	1.7	0.2-12.9	0.63
Colinet score >9	1.7	0.4-4.0	0.68	1.2	0.4-3.8	0.74
Charlson score >3	2.2	0.8-6.1	0.12	1.9	0.7-5.1	0.22
Progression ≤6 months	1.1	0.4-2.9	0.91	1.4	0.6-3.5	0.48
Death ≤6 months	1.2	0.5-3.1	0.64	1.4	0.5-4.1	0.59

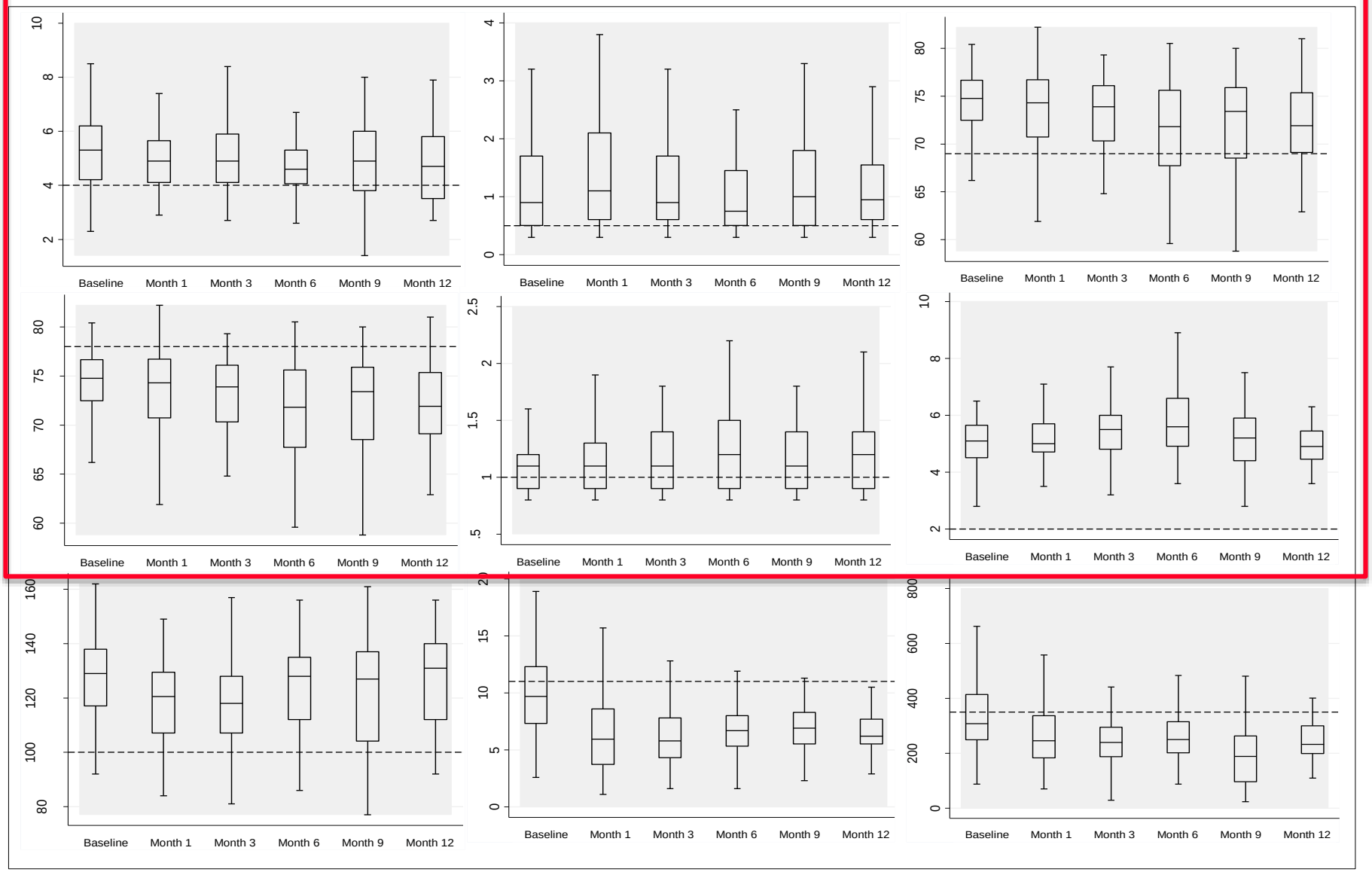
Biomarker (baseline): prediction for TE

Risk factor	All (n=129)			Chemotherapy (n=93)		
	sHR[a]	95%CI	P	sHR[a]	95%CI	P
NLR ≥2.5	0.9	0.3-3.3	0.94	1.6	0.3-7.0	0.57
NLR ≥5.0	0.4	0.1-1.1	0.07	0.4	0.1-1.2	0.11
PLR ≥150	1.3	0.3-5.1	0.69	2.4	0.5-12.3	0.30
PLR ≥300	0.7	0.2-2.5	0.59	0.9	0.3-2.9	0.90
Haemoglobin <100g/L	0.7	0.1-4.6	0.70	1.2	0.2-7.3	0.84
White cell count ≥11.0x10^9/L	0.9	0.3-2.4	0.82	0.9	0.3-2.5	0.86
TEG-MA ≥69mm	1.8	0.8-2.4	0.68	1.2	0.4-3.7	0.71
TEG-Angle ≥77 degrees	1.7	0.6-4.7	0.34	1.7	0.6-5.0	0.34
TEG-R ≤4.5min	1.8	0.7-4.9	0.20	1.3	0.5-3.7	0.60
TEG-K ≤0.9min	1.5	0.5-4.4	0.47	1.5	0.5-4.8	0.46
TEG-R ≤4.5min + TEG-K ≤0.9min	**2.8**	**0.9-8.7**	**0.08**	1.8	0.5-6.0	0.34

Risk Factors for TE

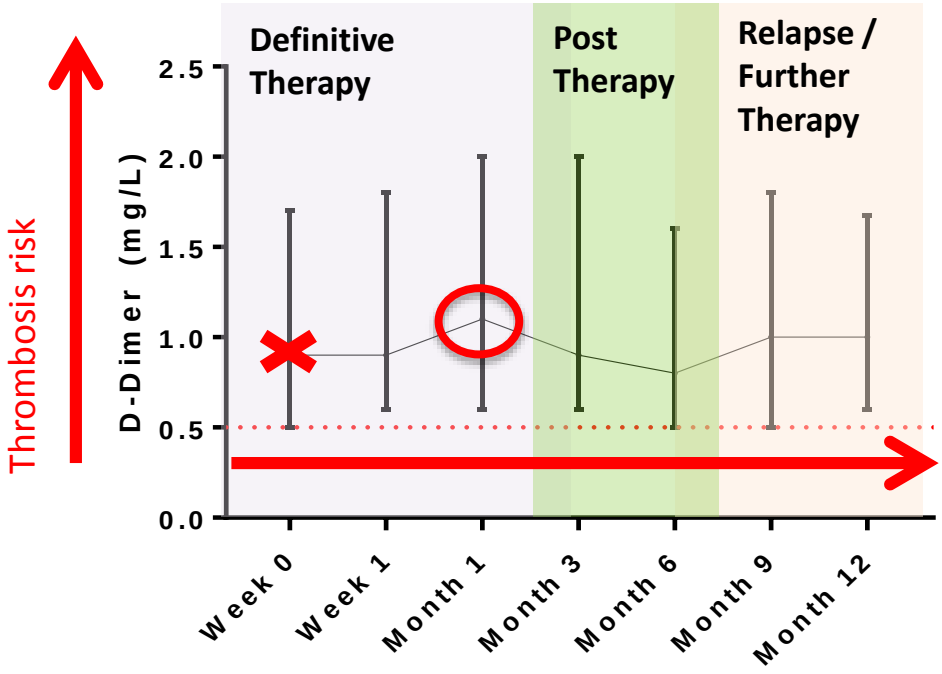
Risk factor	All (n=129)			Chemotherapy (n=93)		
	sHR[a]	95%CI	P	sHR[a]	95%CI	P
Baseline d-dimer ≥0.5mg/L	All events in high risk group			All events in high risk group		
Baseline d-dimer ≥1.5mg/L	1.6	0.6-4.4	0.38	2.1	0.8-5.8	0.16
Month 1 d-dimer ≥1.5mg/L	1.6	0.6-4.4	0.33	1.6	0.6-4.6	0.35
Baseline d-dimer ≥1.5mg/L or month 1 ≥1.5mg/L	**2.6**	**0.8-7.7**	**0.10**	**3.1**	**1.0-9.8**	**0.05**
Baseline platelet count ≥350x10^9/L	1.2	0.5-3.3	0.69	1.5	0.6-4.1	0.40
Month 1 platelet count ≥350x10^9/L	1.7	0.6-4.7	0.27	2.3	0.8-6.5	0.10
Baseline fibrinogen ≥4.0g/L	1.2	0.3-4.3	0.80	1.4	0.4-5.5	0.60
Baseline fibrinogen ≥6.0g/L	0.9	0.3-2.5	0.85	1.0	0.3-3.0	0.97
Month 1 fibrinogen ≥6.0g/L	1.5	0.6-4.3	0.40	2.3	0.8-6.6	0.11
Baseline d-dimer ≥0.5mg/L + fibrinogen ≥4.0g/L	**2.1**	0.5-7.8	0.29	2.7	0.7-10.8	0.16
Baseline d-dimer ≥0.5mg/L + fibrinogen ≥4.0g/L, or baseline d-dimer ≥1.5mg/L	**6.1**	**0.8-49.0**	**0.09**	**8.5**	**1.0-71.4**	**0.05**

Biomarkers: longitudinal profile



BIOTEL

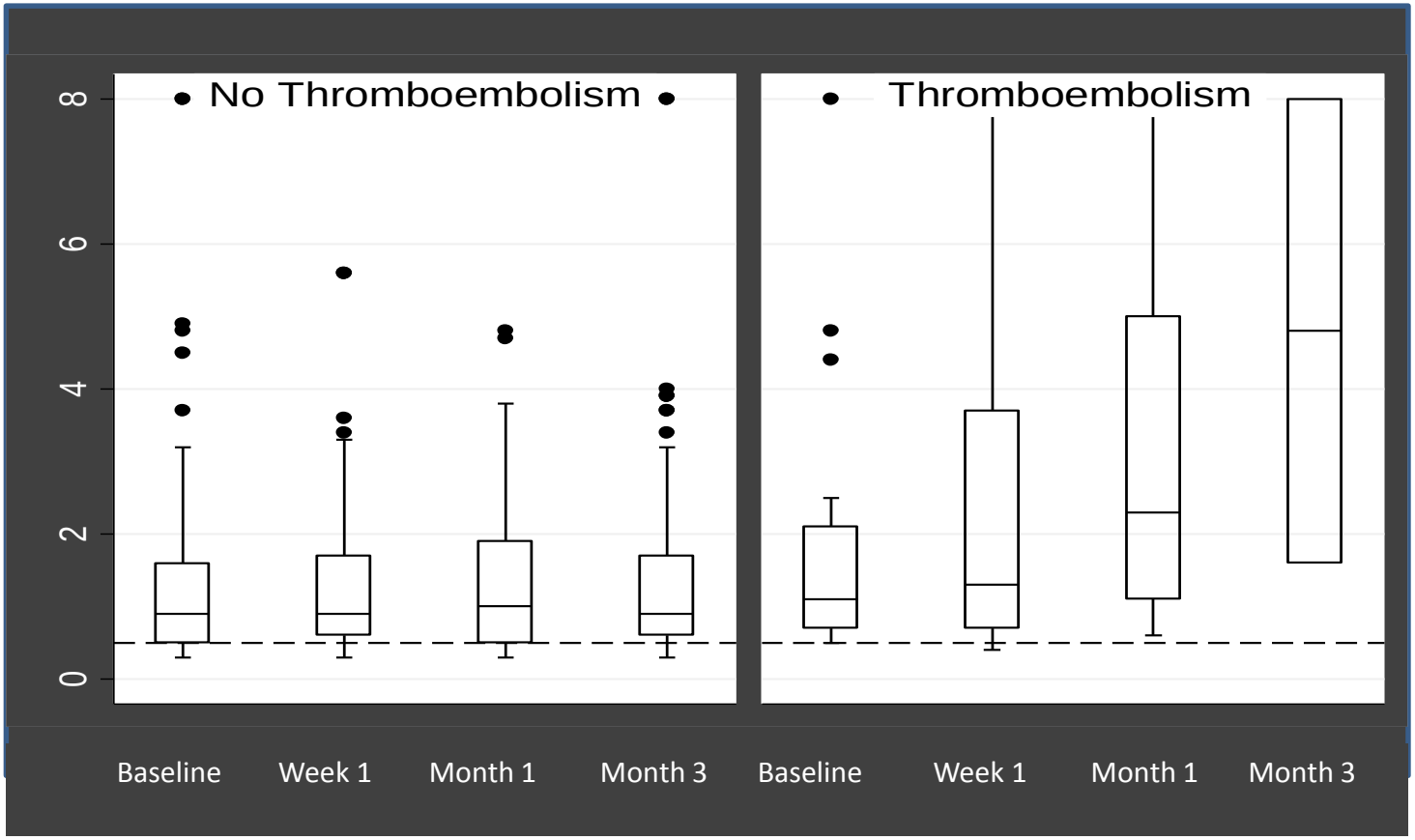
Longitudinal assessments: Identified high risk patients and time periods in which to direct preventative interventions



Dynamic risk assessment

BIOTEL

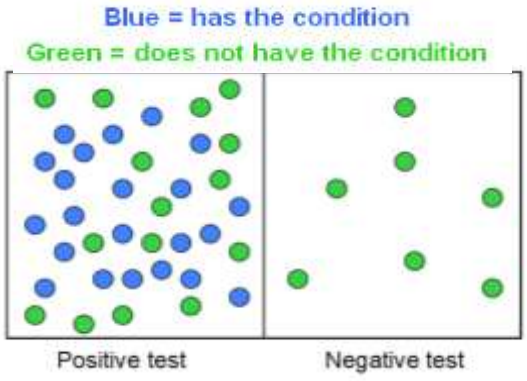
Longitudinal profile: Patients-TE characterised by progressive increase D-dimer and fibrinogen - sensitive and potent predictors of TE



BIOTEL

TE RISK ASSESSMENT MODEL:

- **High Risk - baseline:**
  - Fibrinogen ≥4g/L and d-dimer ≥0.5mg/L; or
  - D-dimer ≥1.5mg/L
- **High versus low risk:**
  - **HR for TE 8.0 (p=0.04)** [vs 1.3 (p=0.68) using est risk score].
  - HR for lung cancer progression: 2.31 (p<0.01)
  - HR for death: 2.54 (p<0.01)
- Incorporation **on-treatment D-dimer (≥1.5mg/L, week 4): 100% sensitivity and 27% PPV**



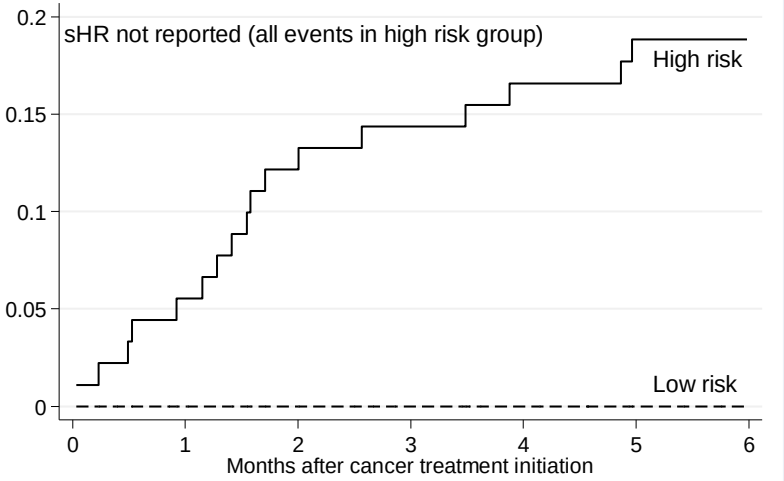
Fibrinogen | D-Dimer

Sensitivity: 100%
Specificity: 34%
NPV: 100%
PPV: 27%

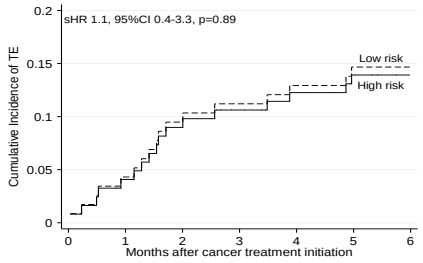
Khorana, A. A., et al. Blood 2008

Model: Comparative Performance – prediction TE

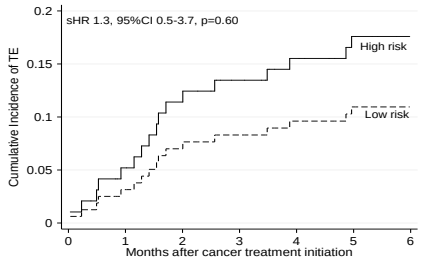
Khorana, CATS, PROTECHT, CONKO



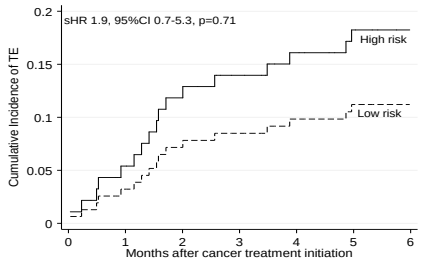
Study derived model



Khorana



PROTECHT



CONKO

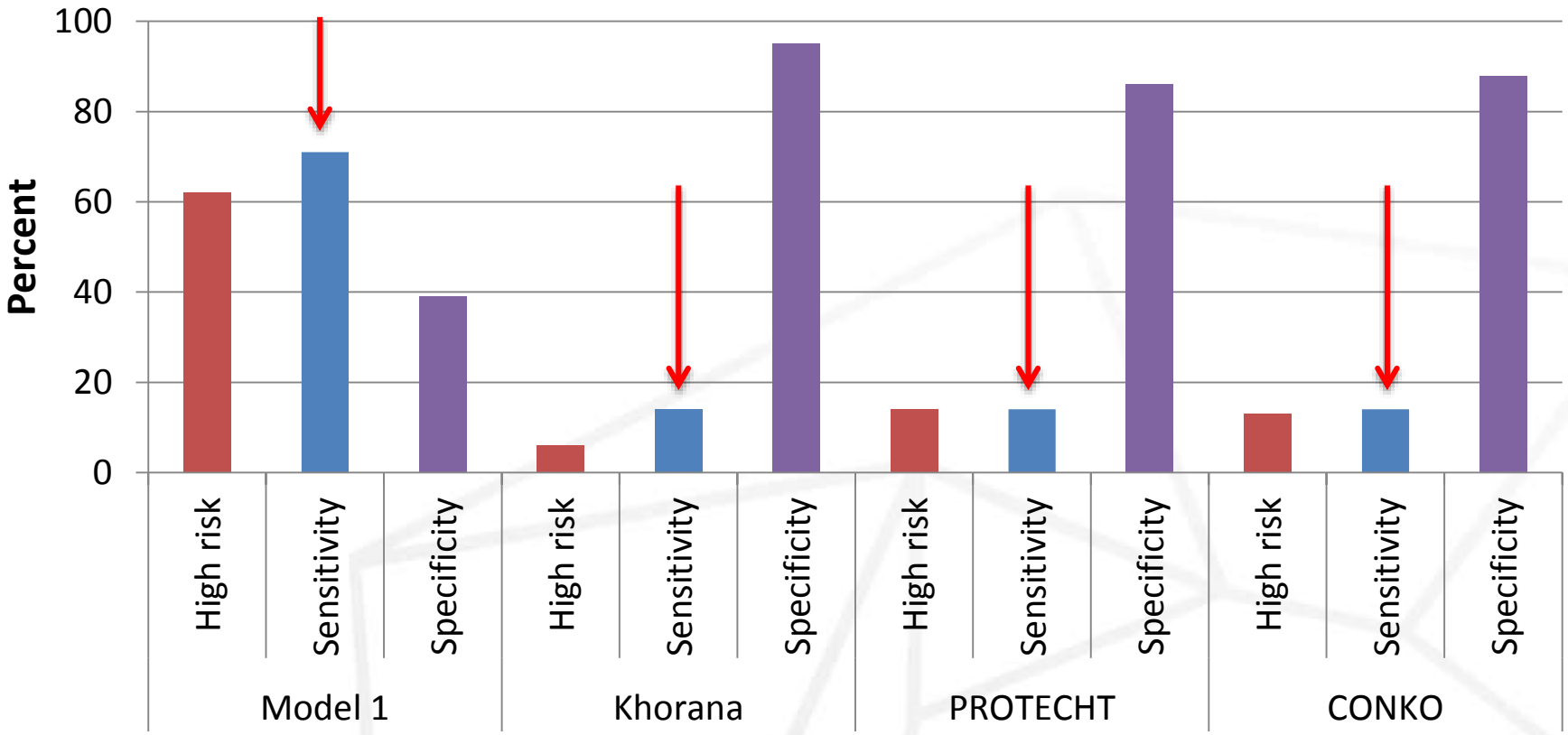
Model: Comparative Performance – predicton TE

Khorana, CATS, PROTECHT, CONKO

Risk Model	TE Cum. %		Prediction of Thromboembolism						
	High Risk	Low Risk	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	sHR (95%CI), p-value	BIC	AUC (95%CI)
Model 1	**26.5**	**0.0**	**100 (79-100)**	**34 (23-47)**	**27 (16-40)**	**100 (85-100)**	**All TE (high risk)**	**127**	**0.67 (0.61-0.73)**
Khorana	20.2	18.9	25 (7-52)	76 (64-86)	20 (6-44)	81 (69-90)	1.1 (0.4-3.3), p=0.89	143	0.51 (0.39-0.63)
PROTECHT	20.9	16.3	69 (41-89)	37 (26-50)	21 (11-34)	83 (65-94)	1.3 (0.5-3.7), p=0.60	142	0.53 (0.40-0.66)
CONKO	25.0	13.8	63 (35-85)	55 (43-67)	25 (13-41)	86 (72-95)	1.9 (0.7-5.3), p=0.71	141	0.59 (0.45-0.73)
CATS	-	-	64 (NR)	82 (NR)	20 (NR)	97 (NR)	-	-	-

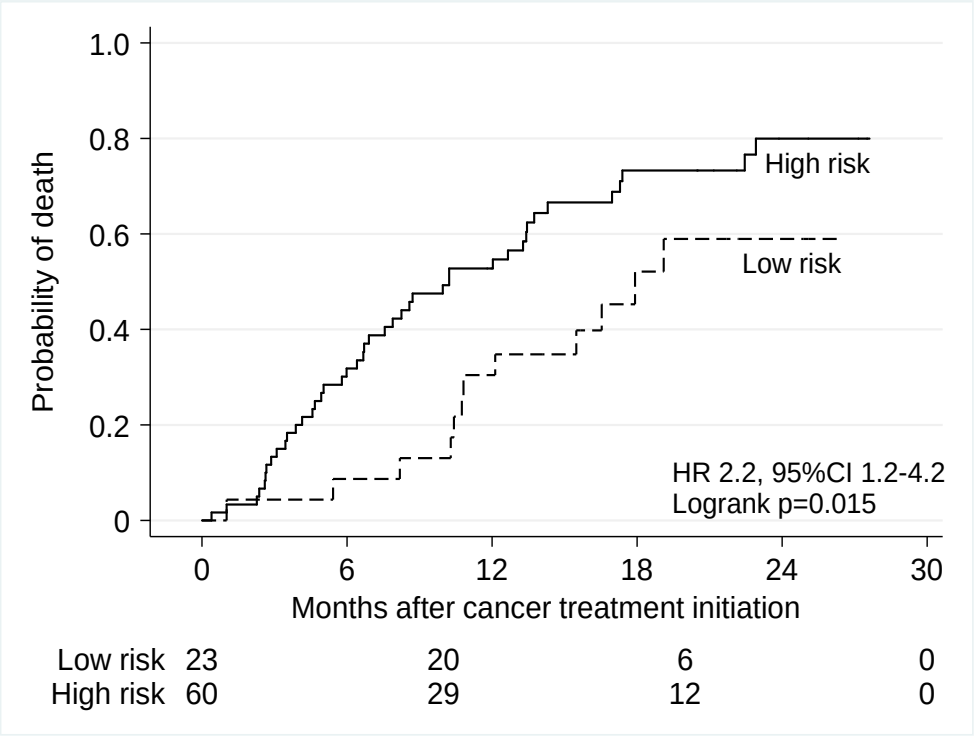
GI Cancer – TE risk model validation

N= 17/171 (10%) experienced TE

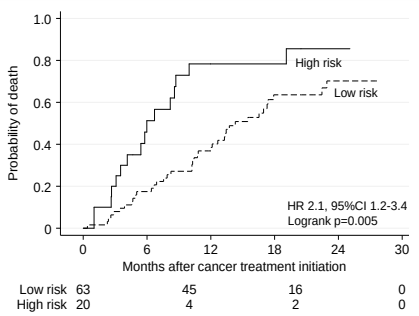


Models: OS

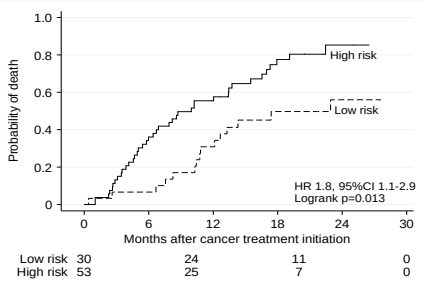
Khorana, CATS, PROTECHT, CONKO



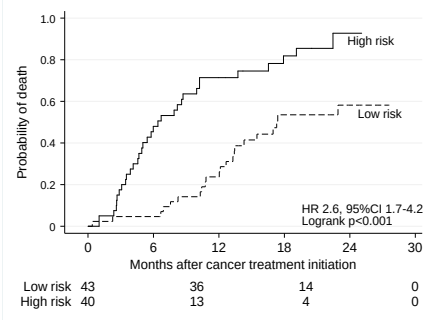
Study derived model
****independent of stage****



Khorana



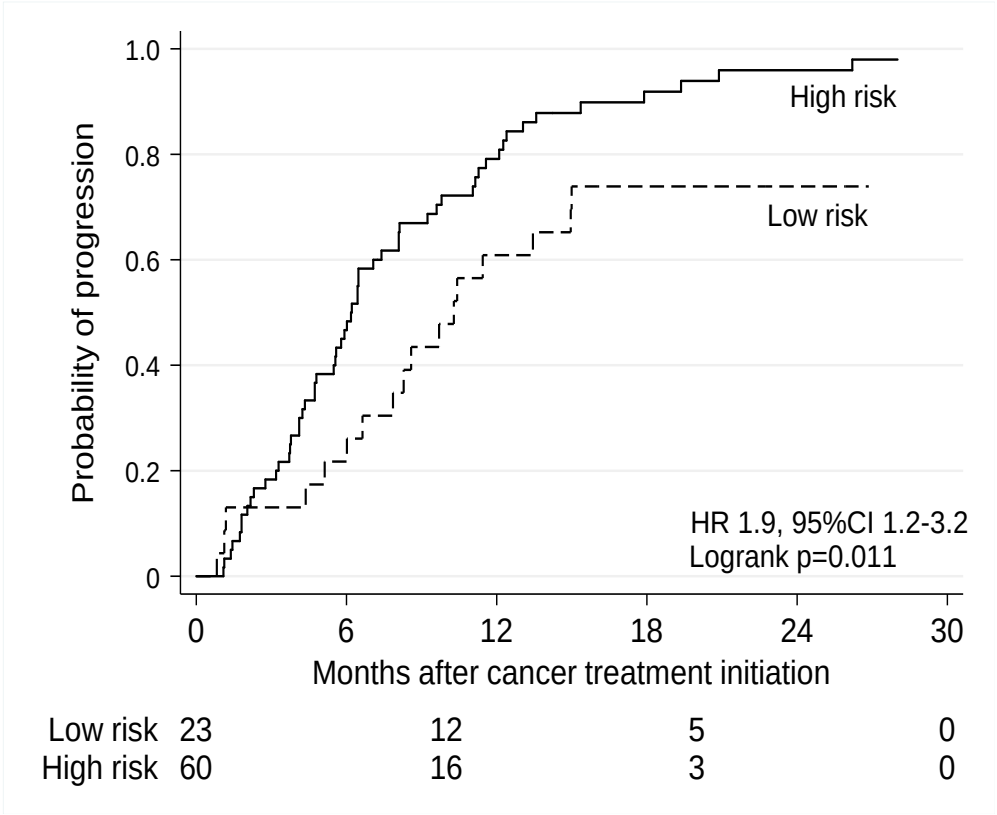
PROTECHT



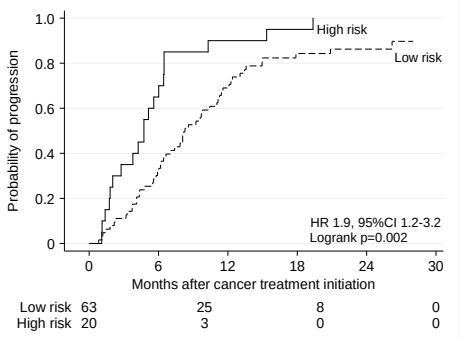
CONKO

Models: PFS

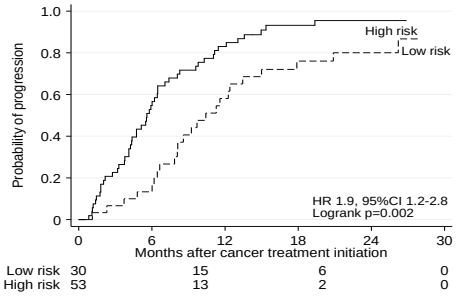
Khorana, CATS, PROTECHT, CONKO



Study derived model
****independent of stage****



Khorana



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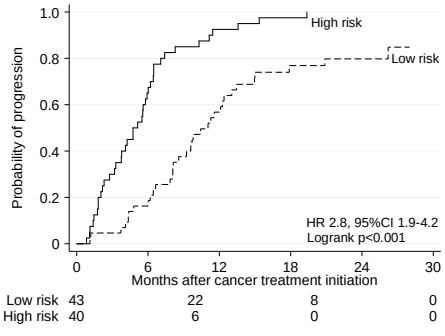
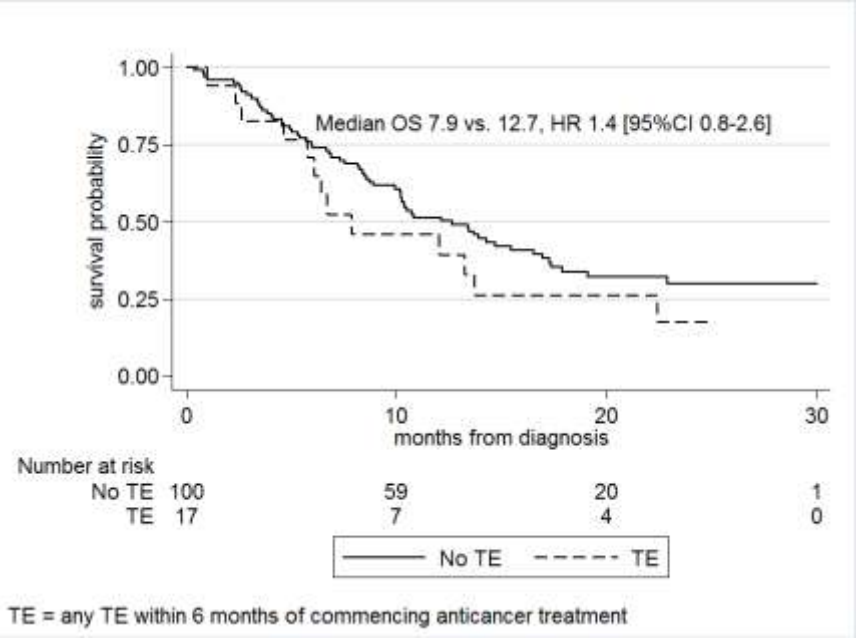
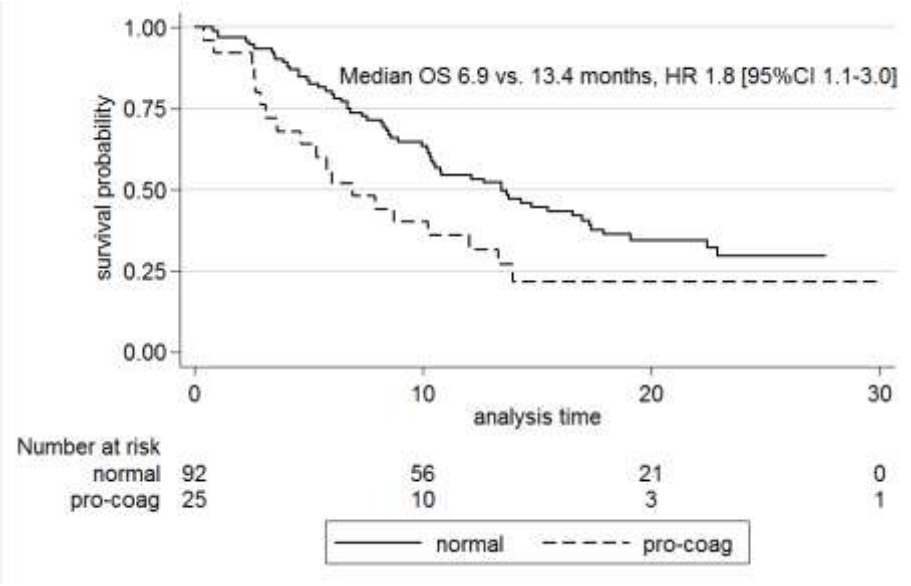


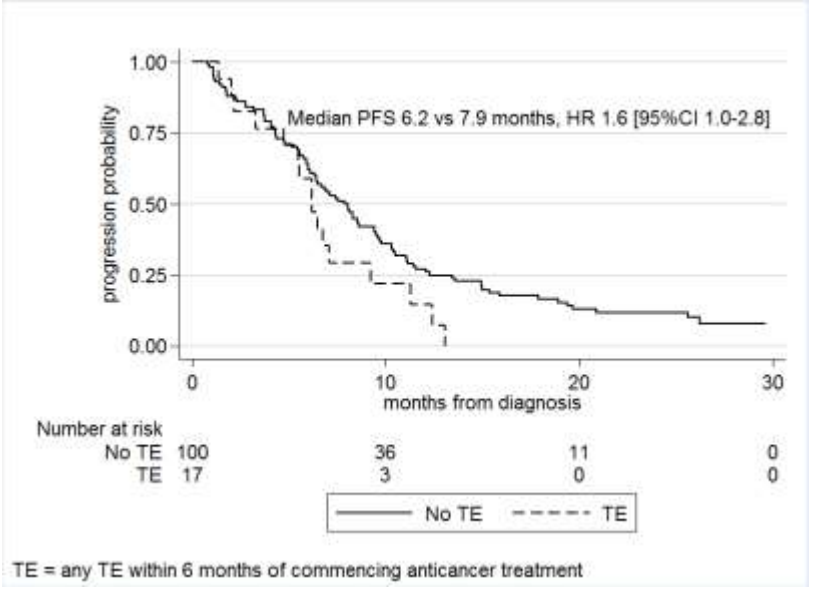
CONKO

Survival curves according to: 1. TE event and 2. Procoagulant state



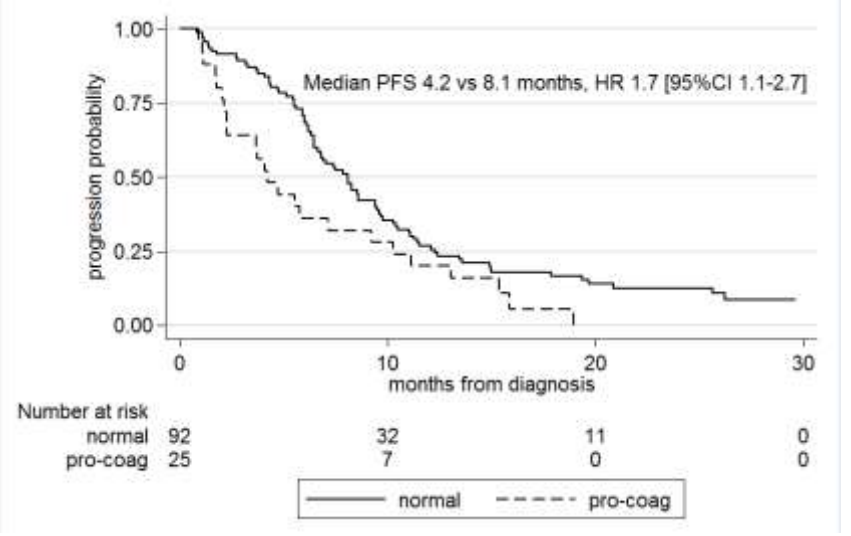
TE = any TE within 6 months of commencing anticancer treatment





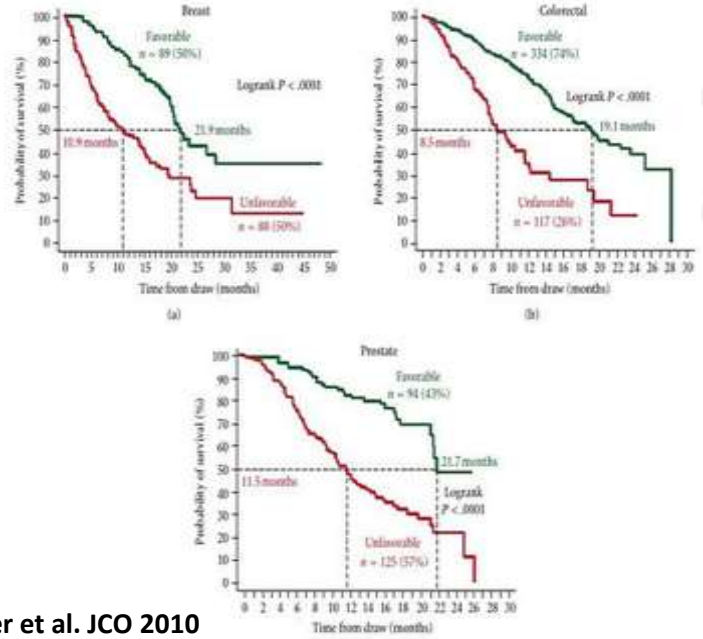
TE = any TE within 6 months of commencing anticancer treatment

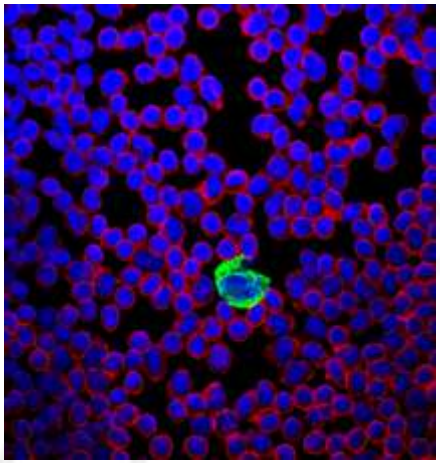
Procoagulant: Fib≥4; D-D ≥1.5; TEG-MA ≥69

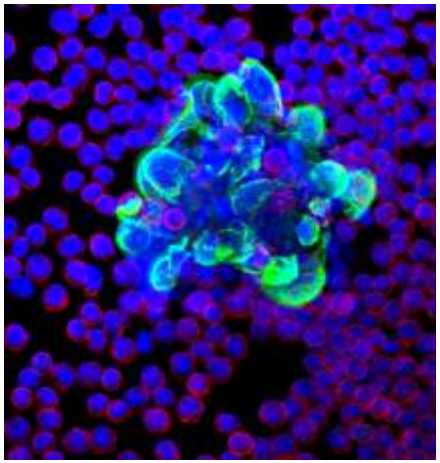


Circulating tumour cells:

- Source tumour re-emergence and distant spread
- Biology – vascular circuitry and coagulation pivotal
  - Intra- and extravasation
  - Re-colonisation, neo-angiogenesis, self-renewal, growth
  - Maintenance of microenvironment
- Coagulation activation: Evasion of “immune surveillance”







Miller et al. JCO 2010

BIOTEL – lung cancer: Discussion

- TE remains frequent with highest risk period in **first 3 months** of starting therapy
- **Dynamic risk:** profile longitudinal thrombogenic biomarkers
- Biomarkers: **elevated D-dimer and fibrinogen** were associated with TE, cancer progression and reduced survival.
- Prioritised biomarkers: used real-time, any patient, at any time
- Applicability in other tumour groups – next phase is to assess the ability to direct targeted preventative interventions.
- Understanding interactions between oncogenes, cancer biology, “coagulation” proteins remains important

Translation into clinical care

RISK TARGETED P-TP

PIII, multicentre RCT assessing targeted pharmacologic thromboprophylaxis in patients receiving anticancer therapies

CASSINI: https://clinicaltrials.gov/ct2/show/NCT02555878
AVERT: https://clinicaltrials.gov/ct2/show/NCT02048865

Collaborative clinical and translational studies

Circulating tumour cells, coagulation activation and biomarkers

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- Sue Wilson
- Philip Smart

> 500 patients and their families that have contributed to our projects