Next-generation biomarkers for cancer-associated thrombosis prediction: the role of non-genomic–omics

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ABSTRACT

Prediction of cancer-associated thrombosis (CAT) remains a major clinical challenge. Although genomic data and clinic-genetic scores have advanced understanding, they do not explain all inter-individual variability in CAT risk. Non-genomic omics, including proteomics, transcriptomics and epigenomics, capture complementary, dynamic biological information that can improve risk stratification. In summary, genomics contributes one piece of a much larger puzzle, necessary, informative, but fundamentally insufficient when used alone to understand, predict or manage CAT. This review synthesizes recent evidence on these non-genomic–omics for CAT prediction, highlights current limitations (validation, standardization, causal inference) and outlines priorities for translational development and clinical validation.

Key words: cancer-associated thrombosis; omics; personalized medicine.

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Introduction

Cancer-associated venous thromboembolism (CAT) remains a major cause of morbidity and mortality in patients with malignancy and presents a heterogeneous risk landscape that challenges one-size-fits-all preventive strategies. Traditional clinical risk assessments (for example the Khorana score) use available tumour and haematological variables but show only moderate discrimination, and a large fraction of CAT events occur outside categories deemed "high risk" by these tools.[1,2] This performance gap has motivated the incorporation of inherited genetic susceptibility into prognostic models with the objective of improving discrimination, calibration and patient selection for primary thromboprophylaxis.[3,4]

The biological rationale for genomic enrichment of CAT prediction is twofold. First, genome-wide and candidate-gene studies have established that common and rare inherited variants modulate baseline venous thromboembolism (VTE) susceptibility in the general population,[5] beyond the classical single-locus tests for factor V Leiden (FVL) or prothrombin G20210A (FII). Second, cancer and its treatments may interact with host prothrombotic genotype to unmask or amplify thrombogenic pathways. Accordingly, a larger development and independent validation effort (the ONCOTHROMB score[4]) used prospective Spanish derivation cohorts with an independent validation in the Vienna Cancer and Thrombosis Study (CATS) population in order to aggregate individual variant effects into clinically actionable risk strata.[4] This score integrates a Genetic Risk Score with nine genetic variants together with tumor site, TNM stage and BMI >25 $kg \cdot m^{-2}$, and outperformed the Khorana index in both derivation and validation samples (reported AUCs in derivation ≈0.78 v 0.58 and consistent superiority on external validation). These results strengthened the evidence that genomic markers convey incremental prognostic information across heterogeneous tumor types and settings.

Despite encouraging discrimination gains, several pragmatic and methodological issues must be emphasized before broad clinical implementation. First, the incremental net clinical benefit of genomic-guided prophylaxis has not yet been established in prospective randomized trials that allocate prophylaxis using a genomic-enriched risk threshold; model performance improvement (AUC increase) does not automatically translate into improved patient outcomes if bleeding risk or implementation barriers negate any VTE reduction. Randomized trials of primary prophylaxis in ambulatory cancer patients (for example nadroparin) illustrate both the potential and the complexity of prophylactic approaches in this population.[6] Moreover, contemporary guidance about primary prophylaxis in ambulatory cancer patients (including guidance on direct oral anticoagulants) underscores the need to balance benefit and harm and to select the appropriate target population.[7,8] Second, many published genomic-clinical models derive from European cohorts with variable tumor mix and follow-up; therefore, trans-ethnic performance, calibration across tumor subtypes, and cost-effectiveness in routine oncology pathways require further study.

In summary, multilocus genomic scores integrated with concise clinical covariates (exemplified by ONCOTHROMB[4]) represent a biologically plausible and empirically supported advance in CAT risk stratification. However, they represent static host predisposition and do not capture the dynamic nature of CAT that other layer of biological information, such as transcriptomics or epigenomics, do. Focus on multi-omics approach (Figure 1) might be the next generation of biomarkers to improve discrimination, uncover mechanistic pathways, and better personalize primary thromboprophylaxis for patients with cancer.

Why genomics is not enough: the dynamic component of CAT risk

CAT is a paradigmatic example of a complex, dynamic phenotype in which genomics is necessary but far from sufficient to explain risk, mechanisms or clinical behavior. Although germline variants such as FVL or FII and numerous GWAS-identified loci contribute to baseline VTE susceptibility in the general population,[5],the proportion of risk they explain in cancer patients is modest when compared with the far more powerful, time-varying drivers that characterize oncological disease.[8,9] Germline and somatic genomics identify predisposition and mechanistic pathways, but they do not measure the proximate processes that actually initiate thrombus formation in a given patient at a given time, since cancer patients experience fluctuating inflammatory states, therapeutic exposures and tumor-derived procoagulant activity, none of which is captured by static genomic data alone. This limitation becomes evident when examining tumor-driven mechanisms: tissue factor (TF) expression, release of TF-positive extracellular vehicles (EVs), platelet activation, neutrophil extracellular traps (NETs), endothelial injury and cytokine-mediated hypercoagulability are all key mediators of CAT; many of these processes have been described in mechanistic and clinical studies.[9-12] These mechanisms are regulated at the transcriptional and post-transcriptional levels and are responsive to microenvironmental cues (hypoxia, cytokines) and to therapy, phenomena that are inherently dynamic and therefore not fully predicted by DNA sequence alone.[11]

The clinical environment, on the other hand, has a major and often overriding influence. Factors such as tumor type and stage,[4] chemotherapy, antiangiogenic therapy, surgery, central

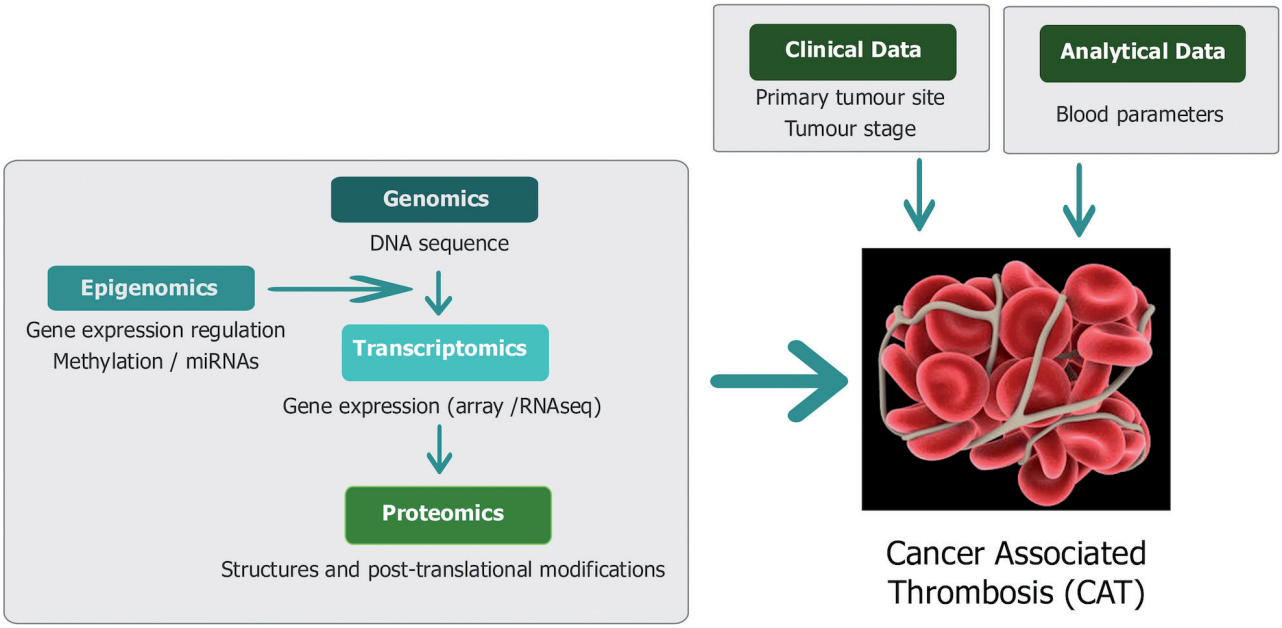

Figure 1. Layers of biological information.

venous catheters, hospitalization and reduced mobility can exert a far more immediate thrombogenic pressure than genomic predisposition.[13] Although validated genomics-clinical tools such as the ONCOTHROMB score[4] outperform clinical-only approaches (such as Khorana score), other validated risk models and systematic reviews emphasize that clinical stratification remains essential for decision-making.[13-15]

Circulating biomarkers offer another clear illustration of the dynamic component of CAT risk: elevations in D-dimer, factor VIII, prothrombin fragments (F1+2), fibrinogen, and parameters of thrombin generation consistently predict near-term VTE in cohorts of cancer patients.[9,10,16,17] These biomarkers directly report the activation state of coagulation and inflammation and therefore provide predictive information that is complementary to, and often more proximate than, information derived from germline or single-timepoint somatic genotyping.

A clinically instructive example that encapsulates the gap between genomics and dynamics is the observation of increased thrombotic events in non-small cell lung cancer patients with ROS1 rearrangements. Multicenter data show an association between ROS1 rearrangement and a higher incidence of thromboembolic events,[18] but this study also report that D-dimer levels, disease burden, systemic inflammation and treatment exposures modulate which ROS1-positive patients suffer thrombosis. In other words, the oncogenic rearrangement identifies a mechanistic propensity, but the dynamic clinical and biomarker milieu determines event occurrence and timing.

From a mechanistic and translational research perspective, these observations imply that improving CAT prediction and prevention requires embedding genomics within longitudinal frameworks that capture the dynamic biology, such non-genomic omics data (i.e. transcriptomics or/an epigenomics). Only by integrating static predisposition (genome) with functional, time-resolved dynamic signals can models approach the discrimination needed for individualized prophylaxis and management. In the meantime, the pragmatic message for clinicians is to view genomics as an important component of mechanistic insight (contributing to the understanding of the underlying biological and pathophysiological mechanisms of disease) and long-term risk profiling, but to rely on dynamic clinical assessment and laboratory biomarkers when making near-term prophylactic and diagnostic decisions for patients at risk of CAT.

Non-genomic omics with relevance to CAT

Building on the limitations of static genomics outlined above, we will examine additional, non-genomic omics layers that more directly capture the dynamic biology driving CAT. Specifically, we will consider transcriptomic, epigenomic and proteomic data that can bridge mechanistic insight with dynamics biomarkers and thereby improve short-term risk discrimination and translational applicability.

Proteomics

Proteomics is the large-scale, systematic study of the proteome, the set of proteins expressed by a cell, tissue, or organism, focused on identifying and quantifying proteins, characterizing their structures and post-translational modifications, and mapping their interactions and temporal/spatial dynamics. These objectives are commonly pursued using high-throughput analytical methods such as mass spectrometry and protein-array technologies.

Proteomics offers a direct, functionally proximate window onto the protein-level effectors of thrombogenic biology in cancer patients and therefore has clear potential to improve prediction of CAT beyond static single-timepoint omics. Plasma and extracellular-vesicle (EV) proteomics capture tumor-derived and host inflammatory signals that are temporally nearer to thrombus formation (i.e. TF and TF-bearing EV cargo, acute-phase reactants, neutrophil/NET-associated proteins and markers of platelet and endothelial activation).[10,11] Empirical work supports this promise: functional and proteomic analyses of EV-TF activity demonstrate higher EV-associated procoagulant activity in progressive cancers and link EV cargo to coagulation readouts.[11,19] Meta-analytic data also support the association between TF-bearing microparticles and thrombosis risk in cancer patients.[12] Unbiased mass-spectrometry discovery in non-small cell lung cancer (NSCLC) cohorts has identified inflammation- and neutrophil-enriched protein signatures that segregate patients who develop VTE and achieved encouraging discrimination in discovery sets.[20] Translational efforts have moved from discovery to targeted panels and multiplexed assays (coupled with machine-learning approaches[21]) to generate multivariable proteomic risk scores that can be evaluated alongside classical biomarkers (D-dimer, F1+2, thrombin generation) and clinical scores.[19,22] Nonetheless, important constraints remain since many studies are discovery-oriented with modest sample sizes and tumor-specific heterogeneity, assay and pre-analytic variability (particularly for EV isolation and TF activity assays) limit reproducibility, and independent prospective validation across tumor types, treatment contexts and pre-analytic pipelines is required before clinical implementation.[11,23] Proteomics uniquely measures the dynamic, multi-pathway protein effectors that mediate CAT and therefore can materially enrich short-term risk stratification when integrated with clinical variables and established coagulation biomarkers, but realization of its clinical utility depends on rigorous standardization and large-scale validation.[23]

Transcriptomics

Transcriptomics is the large-scale study of the transcriptome, defined as the complete set of RNA transcripts produced by a cell, tissue, or organism under specific conditions, with the aim of analyzing gene expression patterns, transcript structure, and regulation.

Transcriptomic profiling offers a complementary, mechanistically informative and time-sensitive layer of molecular data that can materially improve understanding and short-term prediction of CAT. By measuring gene expression programs in tumor cells, stromal compartments and circulating cells, transcriptomics directly reports the regulatory states that control proximate procoagulant effectors (for example, transcriptional upregulation of tissue factor, chemokines and platelet-related genes, neutrophil activation signatures, and endothelial activation pathways), thus linking oncogenic and microenvironmental

cues (hypoxia, cytokines, therapy) to thrombogenic biology in ways that DNA sequence alone cannot capture.[22,24]

Single-cell and bulk RNA-seq studies can reveal heterogeneity in TF and coagulation-related gene expression across tumor cell populations and identify non-malignant cellular contributors (endothelial cells, tumor-associated neutrophils/monocytes) that express NET- and inflammatory gene modules implicated in thrombosis.[22,24] Empirically, transcriptome-derived signatures have already shown predictive signal: several recent works and reviews point to prothrombotic signatures that include genes such as VWF, PF4 and CXCL8 and that associate with VTE risk in cancer cohorts.[25,26] Transcriptomics also informs mechanisms relevant to extracellular-vesicle biology (e.g., expression of TF and proteases that regulate TF shedding), thereby connecting gene expression to downstream EV cargo and functional procoagulant activity measured in plasma.[12] From a translational perspective, longitudinal transcriptomic sampling (including repeated bulk or single-cell profiling and integration with circulating biomarkers such as D-dimer, EV-TF activity, proteomic panels[19,23]) could capture therapy-induced shifts in thrombogenic programs and improve temporal discrimination of near-term VTE risk; however, practical barriers remain, notably tissue accessibility, intra-tumor and inter-patient heterogeneity, the need for standardized sampling and analytic pipelines, and the requirement for large, independent prospective validations across cancer types and treatment contexts.[27,28]

Epigenomics (DNA methylation, microRNA)

Epigenomics is the comprehensive study of the epigenome, encompassing genome-wide chemical modifications to DNA and histone proteins that do not alter the DNA sequence but influence chromatin structure and gene regulation. Epigenomic mechanisms also involve microRNA (miRNA), a small, endogenous non-coding RNA molecule, typically ~22 nucleotides in length, that regulates gene expression post-transcriptionally by binding to complementary sequences in target messenger RNAs, leading to mRNA degradation or translational repression.

Epigenomics provides a mechanistically coherent and empirically tractable layer of information that can meaningfully contribute to prediction of CAT. DNA methylation governs the accessibility of regulatory elements and thereby shapes transcriptional programs that determine the expression of proximate procoagulant effectors such as TF, cytokines, and proteases that influence extracellular-vesicle (EV) biogenesis and cargo. Because methylation marks are relatively stable compared with mRNA yet reflect tumor lineage and oncogenic epigenetic states, locus-specific or epigenome-wide methylation profiling in tumor tissue (and increasingly in circulating cell-free DNA) can explain inter-tumor differences in inducible thrombogenic programs that are not captured by DNA sequence alone.[29,30] A paradigmatic case derives from glioma biology, where IDH1-mutant gliomas exhibit a CpG island methylator phenotype with hypermethylation of the TF gene promoter, reduced tumoral tissue-factor expression, and a markedly lower observed incidence of VTE compared with IDH1 wild-type glioblastoma.[31]

Complementarily, miRNAs act post-transcriptionally to modulate networks of mRNAs involved in coagulation, endothelial and platelet biology, and innate immune activation; circulating miRNAs measured in plasma therefore offer a minimally invasive, dynamic readout of tumor-derived and host inflammatory states that may change with disease progression or therapy.[32-34]

Empirical work that exemplifies these principles already exists. In the miRNA domain, tumor profiling studies have identified sets of differentially expressed miRNAs associated with subsequent VTE in colorectal cancer and other tumours;[32] targeted plasma miRNA panels in ovarian cancer have interrogated miRNAs that regulate components of the tissue-factor pathway, suggesting candidate circulating signatures.[33] Nevertheless, as in the case of proteomics and transcriptomics, the field remains at an early translational stage since the reviewed evidence indicates methodological heterogeneity and the need for prospective validation and standardization before clinical implementation.[27,28,35]

Other biological layers of relevance to CAT

Other biological layers beyond proteomics, transcriptomics and epigenomics are emerging strongly in the field of omics data that can provide complementary, mechanistically plausible information for predicting CAT. One of them is metabolomics that measures small molecules and lipid species that report the instantaneous biochemical state of tumor, host and microenvironmental metabolism (energy metabolism, amino-acid pathways, lipid oxidation, one-carbon metabolism), and therefore can capture proximate mediators of haemostasias and inflammation that are not visible at the DNA or even mRNA level. Empirical human and experimental work have associated specific metabolic signatures with VTE.[36] Large plasma metabolome–profiling efforts have identified altered carnitines, amino acids (tryptophan, phenylalanine), ketone bodies and lipid species in subjects with incident VTE[37,38] and integrative studies that combine plasma metabolomics with the proteome have begun to map metabolic pathways linked to thrombosis biology.[39] In addition, animal models show that tumor-associated metabolites can promote thrombosis, providing experimental causal evidence.[40]

Other data source that are receiving a lot of attention is the gut microbiome that represents another biologically plausible layer of relevance to CAT because microbial communities shape systemic metabolism and immune tone. Microbiome-derived metabolites (for example, trimethylamine N-oxide and other bioactive small molecules) can influence platelet reactivity, endothelial function and inflammation (pathways that intersect with coagulation).[41,42] Epidemiological, experimental and Mendelian-randomization investigations have reported associations between gut microbial taxa or microbial-linked metabolites and VTE risk.[43] However, current limitations are substantial and well documented. Once again, metabolomic and microbiome studies vary in sample handling, analytic platforms, and bioinformatic pipelines, producing heterogeneity and replication challenges; many published associations are observational and susceptible to confounding, reverse causation and cohort-specific effects; causal inference is only beginning to be addressed; and prospective, well-powered studies that demonstrate incremental clinical utility for CAT prediction remain limited.[28]

Integration of omics data: multimodal models and analytical considerations

When seeking to predict CAT from molecular data, relying on a single omic layer, whether germline genomics, tumor somatic genomics, transcriptomics, proteomics, or epigenomics, is inherently limited because each layer captures only a subset of the biological processes that produce a thrombus. Genomics identifies predisposition and mechanistic pathways, but it is static and does not measure the proximate, time-varying processes that precipitate events in an individual patient at a particular time. Transcriptomics reports regulatory programs but is sensitive to sampling time and tissue. Proteomics measures the effector molecules but is susceptible to pre-analytic variability and may reflect both host and tumor signals. Epigenomics supplies regulatory context but can be tissue- and context-dependent. Each omic thus contributes partial, sometimes complementary information, but none alone captures the dynamic, multi-cellular, therapy-responsive biology that drives near-term VTE.[27]

Integrating multiple omic layers (Figure 1) could address these limitations by combining complementary strengths. A multi-omic model can merge i) static predisposition (germline variants, tumor mutations, epigenetic baseline) with ii) regulatory state (tumor and stromal transcriptomes, methylation), and iii) proximate effectors (plasma proteome, EV cargo, functional coagulation assays such as D-dimer and thrombin generation). This integrated view can increase mechanistic fidelity (linking cause to effect), improves temporal relevance (by incorporating dynamic proteomic and biomarker readouts), and permits multivariate signatures that combine many weak predictors into a stronger, more robust signal.[27,28] In practice, hybrid genomics-clinical tools that incorporate biomarkers outperform purely clinical scores for short-term CAT prediction, illustrating the clinical potential of integrative approaches.[4]

Despite this promise, integrating multiple omics faces important, practical limitations that currently constrain translational impact. First, pre-analytic and assay heterogeneity is a major barrier, including different sample types (tumor tissue, plasma, EV fractions, cell-free DNA), collection protocols, storage conditions, and platform chemistries produce batch effects and measurement noise that complicate cross-study integration.[43] Second, temporal discordance is common, for instances omic layers are often sampled at different times (e.g., archival tumor sequencing *vs* contemporaneous plasma biomarkers), yet CAT risk is time-dependent where models therefore require longitudinal, synchronized sampling to be truly predictive. Third, cohort size, heterogeneity and statistical power limit robust discovery and validation, for example many proteomic/transcriptomic/epigenomic studies of CAT are discovery-oriented with modest VTE case counts and tumor-specific biases, reducing generalizability across cancer types and treatments. Fourth, computational and inferential challenges, such as high dimensionality, multicollinearity, overfitting, interpretability of complex machine-learning models, and the need to calibrate risk scores for clinical decision thresholds.[21,27,28] These limitations complicate development of usable, regulatory-acceptable predictors. Finally, operational and economic constraints (cost, assay throughput, and the need for clinical-grade, reproducible tests) and the absence of prospective, multi-site validation hinder adoption into practice.

In summary, single-omic approaches are constrained by partial, time-limited views of the biology driving CAT; multi-omic integration offers complementary, mechanistically richer, and temporally more relevant information that can substantially improve short-term risk discrimination. However, realization of this promise depends on solving practical problems of standardization, synchronized longitudinal sampling, cohort scale and diversity, robust analytical methods, and demonstration of clinical utility through prospective validation. Addressing these challenges through harmonized protocols, consortia-based studies, targeted assay development, and rigorous modelling/validation pipelines is the path by which multi-omic CAT prediction can move from conceptual promise to clinical reality.

Conclusions

Non-genomic omics (such as proteomics, metabolomics, transcriptomics, epigenomics and microbiome profiling) provide complementary, dynamic biological information with the potential to enhance prediction of CAT beyond genomics alone. Current data are hypothesis-generating and show proof-of-concept for several candidate signals, but prospective validation, methodological harmonization and demonstration of clinical benefit are required before routine adoption. Integrative, multimodal approaches that adhere to rigorous analytic and validation standards represent the most plausible path toward clinically actionable next-generation CAT biomarkers.

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