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Strategic context:

Standardized Medical Name: Cancer-Associated Thrombosis (CAT): Incident Venous Thromboembolism (VTE) in Patients with Active Malignancy

Target Patient Profile:

- **Temporality:** Incident. Patients with a newly diagnosed, objectively confirmed (e.g., radiographic evidence) acute Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE), including both symptomatic and incidental findings.
- **Disease Stage/State:** Active Malignancy. Defined as patients diagnosed with cancer within the past 6 months, those currently receiving systemic anticancer therapy (e.g., chemotherapy, immunotherapy, targeted agents), or those with recurrent or metastatic disease.

Strategic Rationale: Pharmaceutical Relevance (2025-2026):

Cancer-Associated Thrombosis (CAT) remains a leading cause of morbidity and mortality in oncology patients. The management of incident VTE is complex due to the inherently high risk for both recurrent thrombosis and anticoagulant-associated bleeding.

While the standard of care has largely shifted from Low-Molecular-Weight Heparin (LMWH) to Direct Oral Anticoagulants (DOACs; Factor Xa inhibitors such as apixaban and rivaroxaban), significant unmet clinical needs persist. Although DOACs are effective in reducing VTE recurrence, they are associated with a substantially elevated risk of major bleeding and clinically relevant non-major bleeding (CRNMB). This risk is particularly pronounced in high-risk populations, such as those with gastrointestinal (GI) or genitourinary (GU) malignancies, often leading to treatment interruptions or the avoidance of optimal anticoagulation.

The 2025-2026 timeframe represents a pivotal strategic horizon for CAT management due to the anticipated maturation of Phase III data for Factor XI (FXI) inhibitors. This novel class of anticoagulants is hypothesized to "uncouple" thrombosis (pathological clotting) from hemostasis (necessary clotting), offering the potential for effective anticoagulation with a significantly superior safety (bleeding) profile compared to Factor Xa inhibitors.

Industry investment is heavily concentrated in this area, with late-stage programs specifically targeting the treatment of incident CAT:

- **Abelacimab (Novartis/Anthos Therapeutics):** This monoclonal antibody FXI inhibitor, administered as a once-monthly subcutaneous injection, is the most advanced agent for the CAT indication. It is being evaluated in two major Phase III trials:

    - **ASTER (NCT05171049):** Comparing abelacimab to apixaban in the general CAT population.
    - **MAGNOLIA (NCT05171075):** Comparing abelacimab to dalteparin (LMWH) specifically in high-bleeding-risk patients (GI/GU cancers). Pivotal data readouts from these studies are anticipated in the second half of 2026.

- **Competitive Landscape:** The intense focus on the FXI mechanism is further evidenced by advanced programs from BMS/Janssen (Milvexian) and Bayer (Asundexian) in other indications, and Regeneron's announcement of initiating a broad Phase 3 program for their FXI antibodies starting in 2025.

The immediate strategic imperative is to rigorously characterize the current landscape of CAT treatment. As FXI inhibitors approach regulatory submission, robust data on the real-world bleeding rates and recurrence rates associated with the current DOAC standard of care is essential to contextualize the clinical trial results and define the value proposition of these novel, safer agents.

Intended Clinical Application Research Utility:

The primary research utility is to establish contemporary, real-world benchmarks for clinical outcomes (specifically major bleeding, CRNMB, and recurrent VTE) and healthcare resource utilization in patients with incident CAT treated with the current standard of care (predominantly DOACs). This evidence is critical for supporting comparative effectiveness research, Health Technology Assessments (HTA), and market access strategies for the anticipated launch of Factor XI inhibitors (e.g., Abelacimab) in the immediate post-2026 timeframe.

Phenotype Description: Cancer-Associated Thrombosis (CAT): Incident Venous Thromboembolism (VTE) in Patients with Active Malignancy

1. Clinical Condition

Recommended Phenotype: Cancer-Associated Thrombosis (CAT): Incident Venous Thromboembolism (VTE) in Patients with Active Malignancy

Common Synonyms:

- Malignancy-Associated Thrombosis
- Cancer-Associated VTE
- Oncology-Associated VTE

2. Detailed Presentation

Overview: Cancer-Associated Thrombosis (CAT) refers to the development of venous thromboembolism (VTE)—encompassing Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)—in the setting of an active malignancy. VTE is a leading cause of morbidity and mortality in oncology patients. The pathogenesis is multifactorial, driven by a hypercoagulable state resulting from tumor-derived procoagulant factors, patient factors (e.g., immobilization), and treatment-related factors (e.g., systemic chemotherapy, surgery, central venous catheters). The management of CAT is uniquely complex due to the high concomitant risks of both recurrent thrombosis and anticoagulant-associated bleeding.

Clinical Presentation and Assessment: The clinical presentation mirrors VTE in the general population. DVT typically presents with unilateral limb edema, pain, and erythema. PE commonly presents with dyspnea, pleuritic chest pain, tachycardia, or, in severe cases, hemodynamic instability. Crucially, a significant proportion of CAT events are **incidental**, discovered during routine imaging for cancer staging or surveillance (e.g., CT scans) in asymptomatic patients. Incidental VTE carries similar clinical significance to symptomatic VTE and requires therapeutic anticoagulation.

Diagnostic Criteria and Findings: Diagnosis of CAT mandates objective confirmation via imaging; clinical suspicion alone is insufficient.

- **DVT:** Compression Ultrasonography (CUS) is the primary diagnostic modality.
- **PE:** Computed Tomographic Pulmonary Angiography (CTPA) is the standard diagnostic test.
- **Laboratory Tests:** D-dimer testing has limited utility in the active cancer population, as levels are frequently elevated due to the underlying malignancy, reducing specificity.

Common Treatments and Medications: The cornerstone of therapy is prompt therapeutic anticoagulation.

- **Current Standard of Care:** Direct Oral Anticoagulants (DOACs), specifically Factor Xa inhibitors (e.g., Apixaban, Rivaroxaban), are the preferred first-line treatment for most patients.
- **Alternative Therapies:** Low-Molecular-Weight Heparin (LMWH) (e.g., Dalteparin, Enoxaparin) remains an important alternative, particularly for patients with very high bleeding risk (e.g., active luminal gastrointestinal malignancies), severe renal impairment, or significant drug-drug interactions.
- **Duration:** Anticoagulation is typically continued for at least 6 months, and often indefinitely as long as the cancer remains active.

Differential Diagnoses and Comorbid Conditions: Differentials include tumor compression of vascular structures, lymphedema, and cellulitis. Key comorbidities influencing management include thrombocytopenia and renal impairment. The site of malignancy is critical; patients with gastrointestinal (GI) or genitourinary (GU) cancers have a substantially elevated risk of bleeding while on anticoagulation, particularly with DOACs.

Prognosis and Complications: Patients with CAT have a poorer prognosis and face significantly higher risks of complications compared to non-cancer patients with VTE.

- **Recurrent VTE:** Risk remains high despite adequate anticoagulation.
- **Bleeding:** Major bleeding and Clinically Relevant Non-Major Bleeding (CRNMB) are frequent complications of treatment. Bleeding events often necessitate the interruption or discontinuation of optimal anticoagulation.

3. Phenotype Boundaries and Granularity

This phenotype is designed to precisely identify a cohort of patients at the onset of VTE occurring concurrently with active cancer, suitable for evaluating the effectiveness and safety of contemporary anticoagulation strategies.

General Exclusions (Out of Scope):

- VTE occurring in patients with a history of cancer who do not meet the criteria for "Active Malignancy."
- Arterial thrombosis (e.g., myocardial infarction, ischemic stroke).
- Isolated superficial vein thrombosis.
- Chronic thromboembolic disease or post-thrombotic syndrome without evidence of a new acute VTE event.
- Patients already receiving therapeutic (rather than prophylactic) doses of anticoagulation prior to the index VTE event.

Temporal Context:

- **Target State:** Incident (Required).

- **Definition:** A newly diagnosed, objectively confirmed (e.g., radiographic evidence) acute DVT and/or PE. Includes both symptomatic and incidental findings.

Clinical Granularity:

- **Severity:** Required. Distinction between DVT (proximal vs. distal) and PE (e.g., massive, submassive, low-risk) is necessary.
- **Acuity:** Required. The event must be acute.
- **Etiology (Active Malignancy Definition):** Required. The VTE must occur in a patient meeting criteria for "Active Malignancy," defined by at least one of the following at the time of the VTE event:
    - Diagnosis of cancer (excluding non-melanoma skin cancer) within the preceding 6 months; OR
    - Currently receiving systemic anticancer therapy (e.g., chemotherapy, immunotherapy, targeted agents); OR
    - Documented recurrent or metastatic disease.
- **Manifestation:** Required. It is critical to identify the specific primary cancer type, with specific attention to high-bleeding-risk sites (Gastrointestinal and Genitourinary malignancies) to allow for appropriate risk stratification. Distinction between symptomatic and incidental VTE is also required.

Population Context:

- Adult patients (≥18 years) with a confirmed solid tumor or invasive hematologic malignancy.

4. Intended Clinical Application Research Utility

The primary research utility of this phenotype is to establish robust, contemporary, real-world benchmarks for clinical outcomes and healthcare resource utilization among patients with incident CAT treated with the current standard of care (predominantly Factor Xa inhibitor DOACs).

This evidence generation is strategically critical due to the anticipated market entry of Factor XI (FXI) inhibitors (e.g., Abelacimab) in the immediate post-2026 timeframe. This novel class of anticoagulants is hypothesized to offer effective anticoagulation with a significantly superior safety (bleeding) profile compared to current therapies.

This phenotype will enable the precise quantification of the real-world incidence of major bleeding, Clinically Relevant Non-Major Bleeding (CRNMB), and recurrent VTE associated with current therapies. This data is essential for contextualizing Phase III clinical trial data (e.g., ASTER, MAGNOLIA) and supporting subsequent comparative effectiveness research, Health Technology Assessments (HTA), and market access strategies for FXI inhibitors.

Clinical Description: Incident Venous Thromboembolism (VTE)

Synonyms: Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), Venous Thrombosis, Thromboembolism, Blood Clot (colloquial).

1. Clinical Case Definition

Venous Thromboembolism (VTE) is a vascular condition encompassing Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE). It occurs when a thrombus (blood clot) forms within the venous system, most commonly in the deep veins of the legs or pelvis (DVT). A PE occurs if the thrombus, or a fragment of it, dislodges and travels (embolizes) to the pulmonary arteries, obstructing blood flow.

The pathogenesis of VTE is often explained by Virchow's triad: venous stasis (e.g., immobilization, surgery), endothelial injury (e.g., trauma, catheters), and a hypercoagulable state (which may be acquired, e.g., due to malignancy or hormonal therapy, or inherited).

The clinical presentation varies significantly. DVT typically presents with unilateral limb edema, pain, warmth, and erythema. PE commonly presents with acute onset dyspnea, pleuritic chest pain, cough, tachycardia, or, in severe cases, syncope and hemodynamic instability (massive PE). A significant proportion of VTE events may be asymptomatic or minimally symptomatic and discovered incidentally during imaging performed for other indications.

Diagnosis requires objective confirmation, as clinical assessment alone is unreliable. Clinical suspicion and risk assessment (e.g., using the Wells' score) guide the diagnostic pathway.

- **DVT:** Compression Ultrasonography (CUS) is the primary diagnostic modality.
- **PE:** Computed Tomographic Pulmonary Angiography (CTPA) is the standard diagnostic test. Ventilation/Perfusion (V/Q) scanning is an alternative, particularly in patients with contraindications to CTPA (e.g., severe renal impairment or contrast allergy).
- **Laboratory Tests:** D-dimer testing is often used in the initial assessment; while highly sensitive, it has low specificity. A negative D-dimer can effectively rule out VTE in patients with low or intermediate pre-test probability, but an elevated level mandates further imaging.

This phenotype is intended to capture the acute, objectively confirmed VTE event.

2. Phenotype Scope & Granularity

- **Temporal Context:** Incident (Required). This phenotype targets newly diagnosed, objectively confirmed acute DVT and/or PE events, including both symptomatic and incidental findings.

- **Severity:** Inclusive of all severities. Clinical distinction between DVT (proximal vs. distal) and PE (e.g., massive, submassive, low-risk) is relevant within this scope.
- **Acuity / Chronicity:** Acute (Required). The event must represent a new, acute thrombus.
- **Etiology:** All etiologies (Provoked and Unprovoked/Idiopathic). This scope captures the VTE event regardless of the underlying cause (e.g., secondary to surgery, trauma, immobilization, malignancy, hormonal therapy, or idiopathic).
- **Population Context:** General Adult Population. This definition is adaptable for application to specific subgroups (e.g., oncology patients, surgical patients, pregnant patients).

3. Related Conditions & Scope Boundaries

The following conditions are related but are not within the scope of this phenotype definition:

- **Arterial Thrombosis:** Conditions such as myocardial infarction, ischemic stroke, or acute limb ischemia (arterial events) are distinct from venous thromboembolism and are not within scope.
- **Isolated Superficial Vein Thrombosis:** Thrombosis confined solely to the superficial veins (superficial thrombophlebitis), without involvement of the deep venous system, is not within the scope of this DVT/PE phenotype.
- **Chronic Thromboembolic Disease (without Acute Event):** The presence of chronic thrombi, post-thrombotic changes (e.g., scarring, synechiae), or established Chronic Thromboembolic Pulmonary Hypertension (CTEPH) without evidence of a new, acute VTE event is not within the scope of this incident phenotype.
- **VTE Mimics:** Conditions causing symptoms similar to DVT or PE, such as cellulitis, lymphedema, ruptured Baker's cyst, musculoskeletal injury, or external vascular compression, are outside the scope unless an acute intraluminal thrombus is objectively confirmed.

4. Key Complications & Common Comorbidities

This section differentiates the core phenotype (the acute VTE event) from its common clinical consequences or associations.

- **Complications:**
    - Recurrent VTE
    - Post-Thrombotic Syndrome (PTS) (long-term complication of DVT)
    - Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (long-term complication of PE)
    - Bleeding (Major or Clinically Relevant Non-Major, typically secondary to anticoagulation treatment)
- **Common Comorbidities / Major Provoking Factors:**
    - Active malignancy

    - Recent major surgery or trauma
    - Prolonged immobilization or hospitalization
    - Inherited or acquired thrombophilias (e.g., Factor V Leiden, Antiphospholipid Syndrome)
    - Obesity
    - Estrogen-containing therapies (e.g., oral contraceptives, hormone replacement therapy)
    - Pregnancy and the postpartum period

5. Intended Data Sources

This clinical description is intended for building concept sets against real-world administrative claims, electronic health record (EHR) databases, and patient registries. The target data should be standardized to the OMOP Common Data Model. Examples of licensable data sources where this concept set would be applied include:

- **Optum®** (Clinformatics® Data Mart, SES, Pan-Therapeutic)
- **Merative™** (MarketScan® Commercial Claims and Encounters)
- **Veradigm** (Health Verity, Practice Fusion EHR)
- **IQVIA** (AmbEMR, PharMetrics Plus)
- **HealthVerity**