NCCN Virtual Oncology Fellows Program:
New Horizons in Quality Cancer Care™

Wednesday, March 17, 2021
1:15 PM – 2:00 PM EDT

Optimal Management of Venous Thromboembolism in Patients with Cancer

Michael B. Streiff, MD
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

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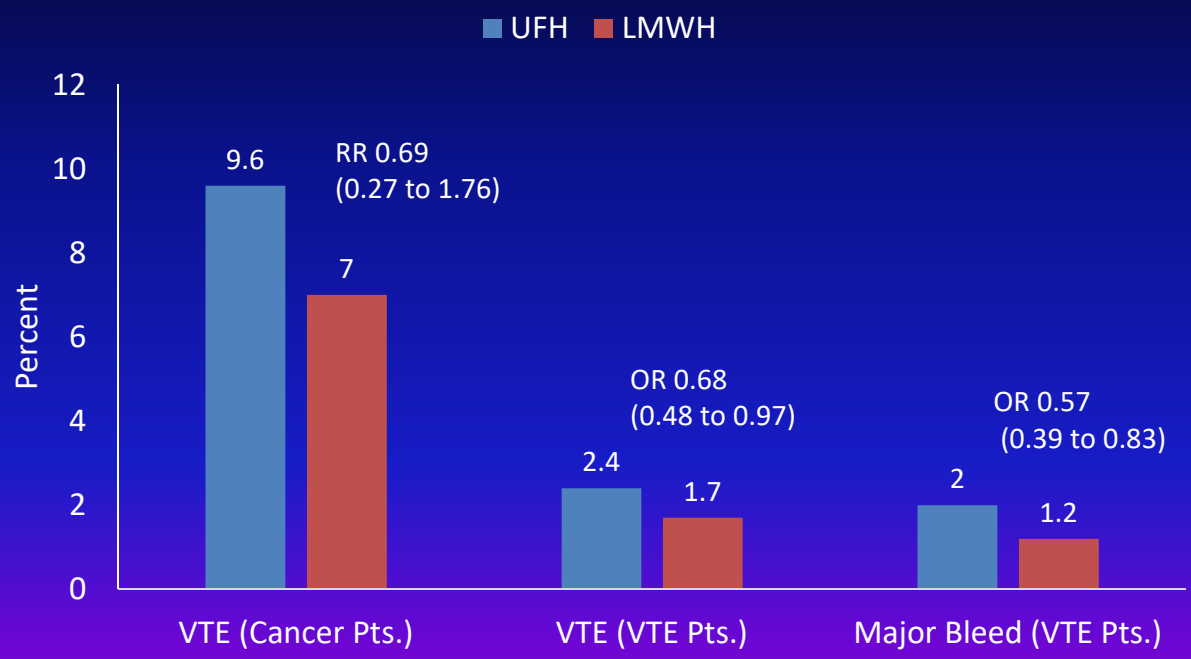
Cancer-Associated Thrombosis (CAT) Therapeutic Anticoagulation Options

- Unfractionated Heparin (UFH)
  - Advantages: short half-life, rapid onset/offset, 100% reversible, easy individualized dosing, OK in renal/hepatic failure
  - Disadvantages: IV administration, frequent lab monitoring, indirect anticoagulant
- Low Molecular Weight Heparin (LMWH)
  - Advantages: longer half-life (4-7 hours), subcutaneous, more predictable weight-based dosing
  - Disadvantages: parenteral, less reversible (60-80%), renal clearance, expensive

Cancer-Associated Thrombosis (CAT) Therapeutic Anticoagulation Options

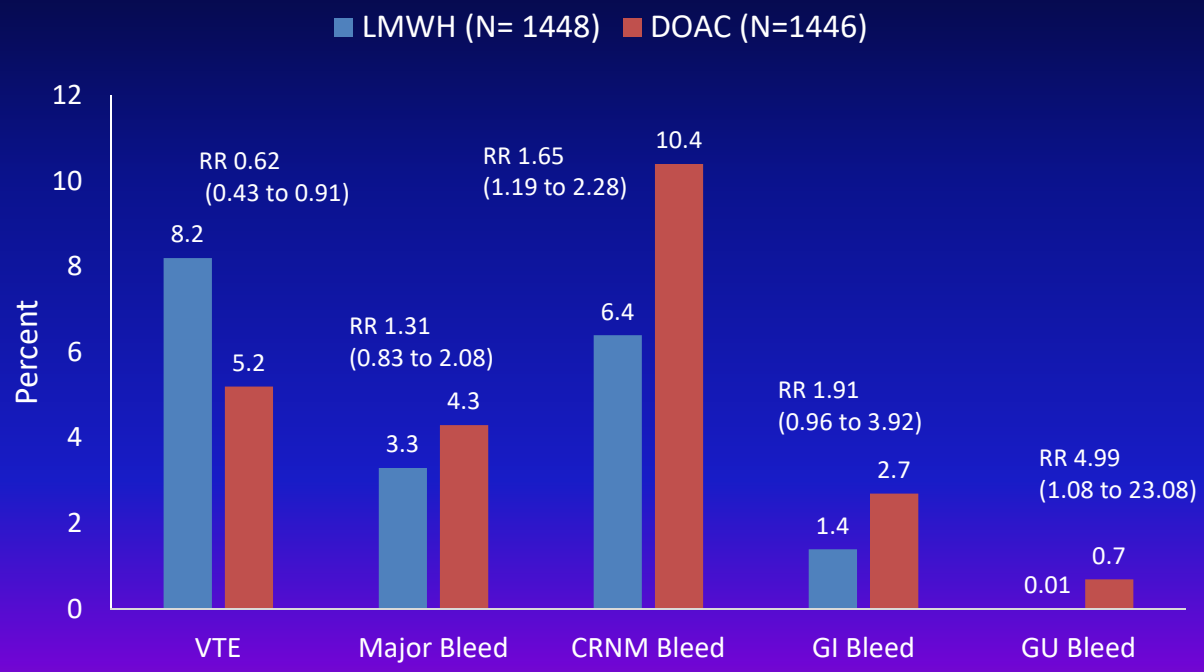
- Direct Oral Anticoagulants (DOACs)
  - Advantages: highly effective, oral, rapid onset/offset, direct anticoagulants, no monitoring necessary
  - Disadvantages: need adequate renal/hepatic function, expensive to reverse, direct anticoagulants, difficult to monitor
- Warfarin (vitamin K antagonists [VKA])
  - Advantages: oral, inexpensive, easy to monitor, can use with poor renal/hepatic function, easy to reverse
  - Disadvantages: less effective, many drug and dietary interactions, frequent monitoring

LMWH is At Least as Efficacious as UFH for Acute Anticoagulation



Hakoum MB, et al. Cochrane Database Syst Rev. 2018 Jan 24;1(1); van Dongen CJ, et al. Cochrane Database Syst Rev. 2004 Oct 18;(4)

LMWH versus DOAC: Outcomes for CAT



Giustozzi M, et al. Thromb Haemost. 2020 Jul;120(7):1128-1136.

CRNM bleed, clinically relevant non-major bleeding; GU, genitourinary

Outcomes with DOACs in CAT

Drug	VTE	Major Bleed	CRNM Bleed	GI Bleed	GU Bleed
Edoxaban v. LMWH (N=1046)	7.9% v. 11.3% HR 0.71 (0.48-1.06)	**6.9% v. 4.0% HR 1.77 (1.03-3.04)**	14.6% v. 11.1% HR 1.38 (0.98-1.94)	**3.8% v. 1.1% HR 3.35 (1.35-8.26)**	1.0% v. 0 HR 11.04 (0.61-199.19)
Rivaroxaban v. LMWH (N=406)	**3.9% v. 8.9% HR 0.43 (0.19-0.99)**	5.4% v. 3.0% HR 1.83 (0.68-4.96)	**12.3% v. 3.4% HR 3.76 (1.63-8.69)**	3.4% v. 2.0% HR 1.75 (0.52-5.89)	0.5% v. 0% HR 3.0 (0.12-73.21)
Apixaban v. LMWH (N=1155)	5.6% v. 7.9% HR 0.63 (0.37-1.07)	3.8% v. 4.0% HR 0.82 (0.40-1.69)	9.0% v. 6.0% HR 1.42 (0.88-2.30)	1.9% v. 1.7% HR 1.11 (0.47-2.58)	0.7% v. 0.2% HR 4.02 (0.45-35.86)

Moik F, et al. Res Pract Thromb Haemost. 2020 May 21;4(4):550-561.

CRNM bleed, clinically relevant non-major bleeding; GU, genitourinary

Anticoagulation Options for Treatment of CAT

- Inpatients: LMWH favored over UFH unless renal failure, high bleeding risk, invasive procedures.
- Outpatients:
  - DOAC favored over LMWH due to similar outcomes, improved adherence and lower cost.
  - LMWH favored if active GI/GU lesions at risk for bleeding or poor hepatic function.
  - Warfarin option if severe hepatic and renal failure.

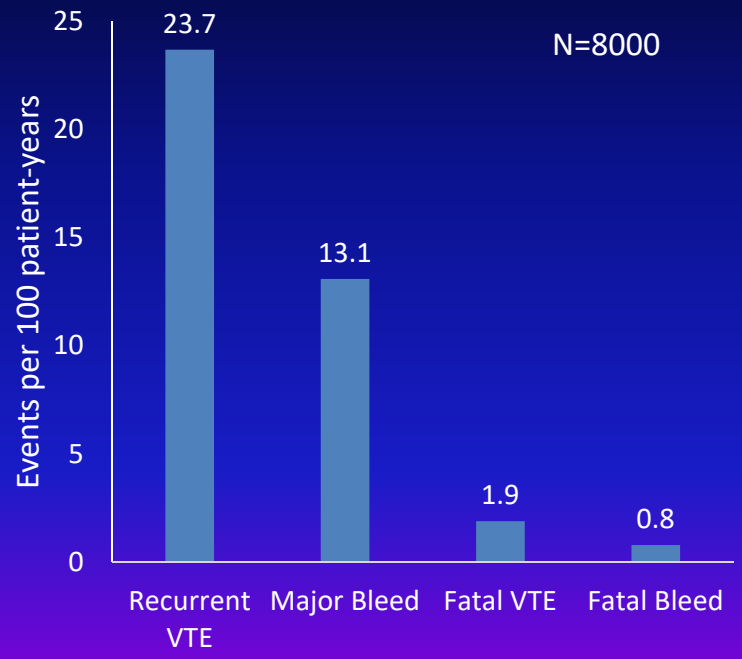
Contraindications to Anticoagulation

- Active bleeding
- High Risk of Bleeding
  - Recent surgery
  - Recent GI Bleed- wait 3-6 weeks before resume anticoagulation
  - Recent CNS Bleed- wait 7-8 weeks to resume anticoagulation
- Heparin-induced Thrombocytopenia
- End of Life Care

Majeed A, et al. Thromb Haemost. 2017 Feb 28;117(3):491-499. Pennlert J, et al. Stroke. 2017 Feb;48(2):314-320.

Cancer Patients at High Risk for Recurrent VTE

- Systematic review of 29 CAT studies 1980-2019
- 15 prospective cohorts, 14 randomized controlled trials (RCTs) with 4786 patient-years follow up
- In cancer patients with CAT on anticoagulation, the risk of recurrent VTE is greater than the risk of bleeding



Abdulla A, et al. Thromb Haemost. 2020 Apr;120(4):702-713.

Anticoagulant Selection in Cancer Patients

- DOACs are first-line agents for anticoagulation in cancer patients
  - Caution in patients with GI/GU malignancies
- LMWH or VKA alternative agents in non-DOAC candidates
  - Proximal GI tract resection
  - Poor renal function (creatinine clearance [CrCl] <30 ml/min)
- Anticoagulation should continue until cancer in remission and no longer on cancer therapy

Which patients are candidates for a DOAC?

- Excellent medication adherence
- No significant drug interactions
  - P-glycoprotein (P-gp) inhibitor/inducers- dabigatran and edoxaban
  - P-gp and CYP3A4 inhibitors and inducers- apixaban and rivaroxaban
- Adequate renal function (estimated CrCl >30 ml/min)
- Adequate hepatic function (<2-3 X ULN)
- Adequate platelet count (at least 50,000/mcL)
- No pregnancy, breast-feeding, antiphospholipid syndrome
- Avoid in gastric bypass surgery

Burnett AE, et al. J Thromb Thrombolysis. 2016 Jan;41(1):206-32.

DOACs in Patients with Morbid Obesity

Study	Patients	Thromboembolism	Bleeding
Kushnir, 2019	366 patients with BMI ≥40 kg/m^2 and VTE	Apixaban 1/47 (2.1%), Rivaroxaban 3/152 (2.0%) Warfarin 2/167 (1.2%)	Apixaban 1/47 (2.1%) Rivaroxaban 2/152 (1.3%) Warfarin 4/167 (2.4%)
Spyropoulos, 2019	2890 matched pairs of patients with morbid obesity and VTE	Rivaroxaban 87 (3.0%) Warfarin 75 (2.6%)	Rivaroxaban 52 (1.8%) Warfarin 73 (2.5%)
Coons, 2020	1840 patients with >100 kg and <300 kg and VTE	DOAC 41/632 (6.5%) Warfarin 77/1208 (6.4%)	DOAC 11/632 (1.7%) War 14/1208 (1.2%)
Cohen, 2020	>19,000 patients with morbid obesity and VTE	Per 100 person years: Apixaban 5.6 Warfarin 7.3	Per 100 person years: Apixaban 4.6 Warfarin 6.2

Kushnir M, et al. Lancet Haematol. 2019 Jul;6(7):e359-e365. ; Spyropoulos AC, et al. Thromb Res. 2019 Oct;182:159-166.; Coons JC, et al. Pharmacotherapy. 2020 Mar;40(3):204-210. Cohen A, et al. J Clin Med. 2021 Jan 8;10(2):200.

Anticoagulation for Treatment of VTE in Patients with Brain Tumors

- Patients with brain tumor(s) at high risk for VTE (15 per 100 person years).[1]
- Failure to use anticoagulation for treatment associated with increased risk of recurrent VTE (HR 11.2).[2]
- In patients with metastatic brain tumors, LMWH does not increase the risk of intracerebral hemorrhage [ICH] (20-40%).[3]
- LMWH is associated with 3-fold increased risk of ICH in glioma patients.[4,5]

1. Streiff MB, et al. J Neurooncol 2015. 2. Edwin NC, et al. Thromb Res 2016. 3. Donato J, et al. Blood 2015. 4. Mantia C, et al. Blood 2017. 5. Zwicker J , et al. J Thromb Haemost 2016.

Anticoagulation for Treatment of VTE in Patients with Brain Tumors

- DOACs and LMWH associated with a similar risk of ICH in patients with brain metastases.[1,2]
- DOACs may be associated with a lower risk of ICH compared to LMWH in glioma patients (0/20 vs. 8/47, 17%).[1]
- DOAC should be considered for management of VTE in patients with brain tumors

1. Carney BJ, et al. J Thromb Haemost 2019. 2. Leader A, et al. Blood Advances 2020.

Management of VTE in Cancer Patients with Thrombocytopenia

- Thrombocytopenia does not protect against VTE.[1,2]
- Anticoagulation during thrombocytopenia is associated with high risk of clinically significant (15.2%) and fatal bleeding (3.6%).[1]
- Platelet count alone (10,000-50,000/mcL) imperfect poor predictor of bleeding.[3-6]
  - Risk factors: Hypoproliferative thrombocytopenia, poor renal/hepatic function, medications, platelet dysfunction, history of prior bleed, hematocrit <25%, allogeneic hematopoietic cell transplant, coagulopathy, duration of thrombocytopenia

1. Gerber D, et al. Blood 2008. 2. Labrador J, et al. Haematologica 2013. 3. Kopolovic I, et al. Ann Hematol 2015. 4. Li A, et al. Blood Adv 2017. 5. Samuelson-Bannow BH, et al. J Thromb Thromboly 2017. 6. Houghton DE, et al. Leuk Lymph 2017. 6. Leader A, et al. Crit Rev Oncol Hematol 2018 .

Management of VTE in Cancer Patients with Thrombocytopenia

- VTE recurrence risk is non-linear
- Risk factor for recurrent VTE:
  - Acute VTE (within 1 month) > Non-acute VTE
  - Upper extremity/central venous catheter (CVC) thrombosis versus lower extremity DVT/PE
  - Cancer type and disease extent/activity
- Limitations: Retrospective studies, mixed patient populations, small number of outcome events
- Management of VTE during thrombocytopenia must be individualized balancing risk of bleeding and thrombosis

Kopolovic I Ann Hematol 2015; Li A Blood Adv 2017; Samuelson-Bannow BH J Thromb Thrombolys 2017;Houghton DE Leuk Lymph 2017;Leader A Crit Rev Oncol/Hematol 2018

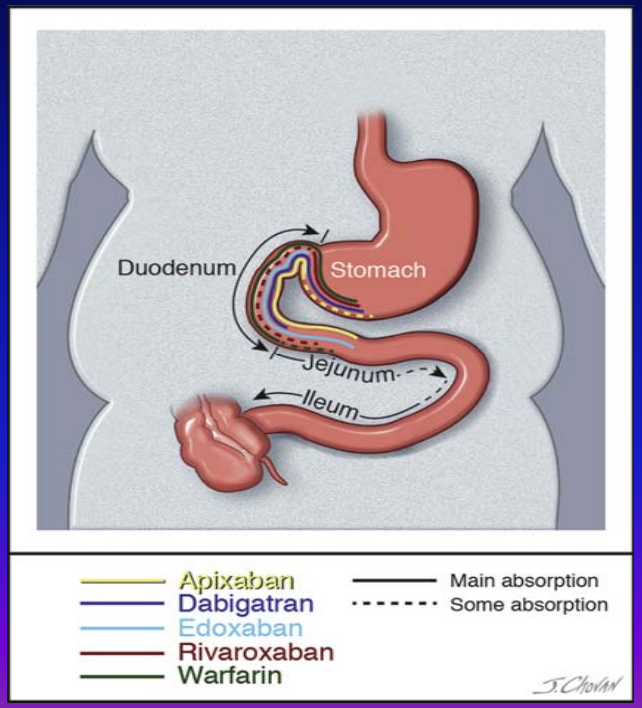
Management of VTE in Cancer Patients with Thrombocytopenia

Risk of Recurrence	Management
High (acute VTE, proximal lower extremity DVT ± PE, recurrent VTE)	• Maintain platelets >50,000/mcL and continue therapeutic anticoagulation with LMWH or UFH • Retrievable IVC filter
Lower (acute distal DVT, CVC-DVT or sub-acute/chronic VTE (>1-3 month[s])	• Therapeutic LMWH with platelets >50,000/mcL • Prophylactic or half-dose LMWH with platelets 25,000-49,000/mcL • No anticoagulation with platelets <25,000/mcL

Samuelson Bannow BT, et al. J Thromb Haemost. 2018 Jun;16(6):1246-1249.

Implications of Cancer Surgery for Treatment of Cancer Associated Thrombosis

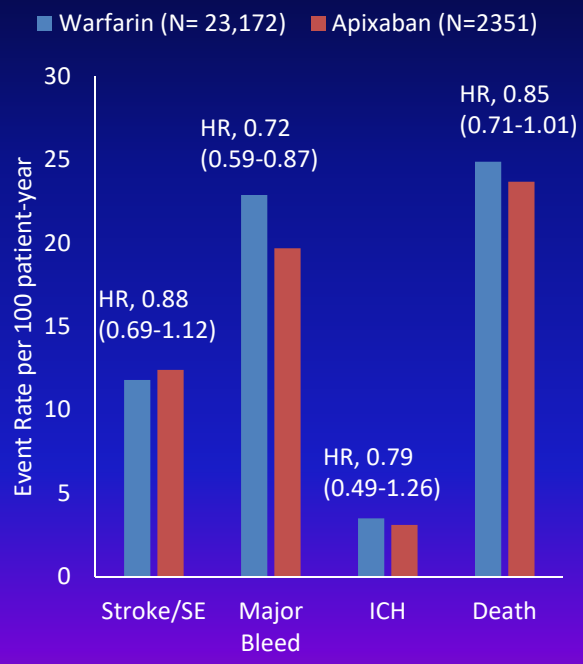
- DOACs are absorbed in the stomach and proximal small bowel
- Proximal GI surgery reduces DOAC absorption
- LMWH remains anticoagulant of choice in cancer patients with proximal GI resections



Martin KA, et al. Am J Med. 2017;130(5):517-524. (Drawings by Joe Chovan)

Can we use apixaban in end-stage renal disease?

- Retrospective cohort of hemodialysis patients with atrial fibrillation
- Propensity score matched analysis
- Thrombotic and bleeding outcomes were similar
- Randomized studies of apixaban in end-stage renal disease (ESRD) warranted



Siontis KC, et al. Circulation. 2018 Oct 9;138(15):1519-1529.

SE, systemic embolism

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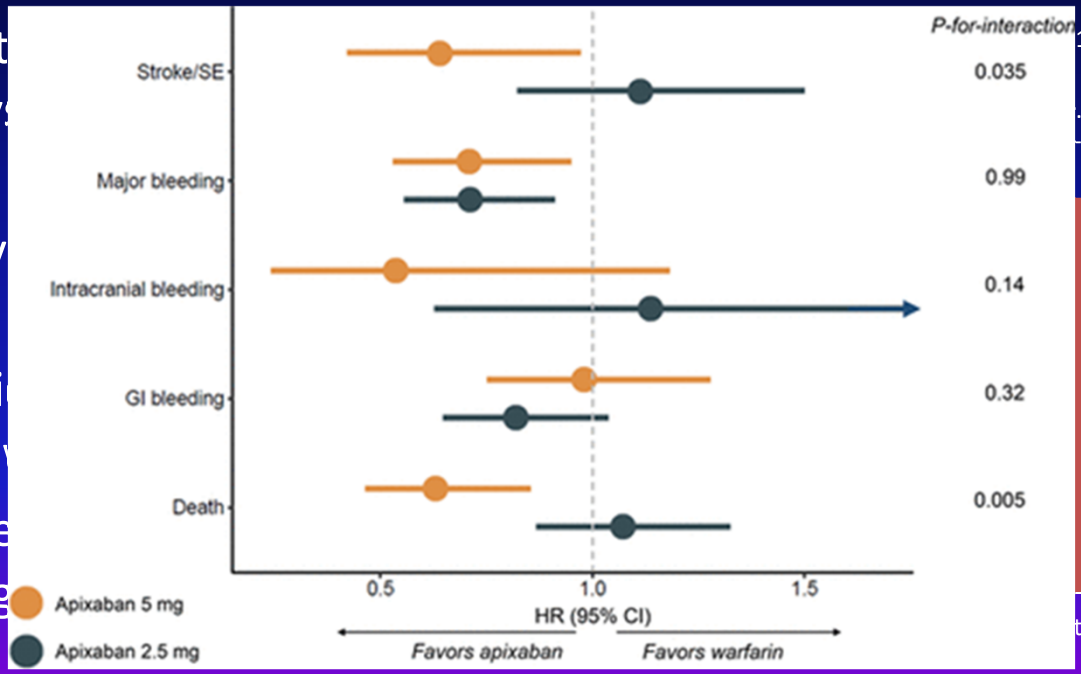

Siontis KC, et al. Circulation. 2018 Oct 9;138(15):1519-1529.

SE, systemic embolism

Failure of Anticoagulation or Recurrent VTE

Reason for failure	Management
Subtherapeutic anticoagulation/non-adherence	Increase INR range, Change anticoagulant
Cancer	Switch to DOAC v. LMWH v. Fonda, increase LMWH dose
Antiphospholipid syndrome	Check Chromogenic factor X-INR correlation, Increase INR target range
Myeloproliferative neoplasm (Polycythemia vera)	Treat myeloproliferative neoplasm
Anatomic vascular compromise (May-Thurner syndrome, Thoracic-Outlet syndrome)	Treat anatomic compression
Heparin-induced thrombocytopenia (HIT)	Direct thrombin inhibitor
Paroxysmal Nocturnal Hemoglobinuria	Eculizumab + anticoagulation

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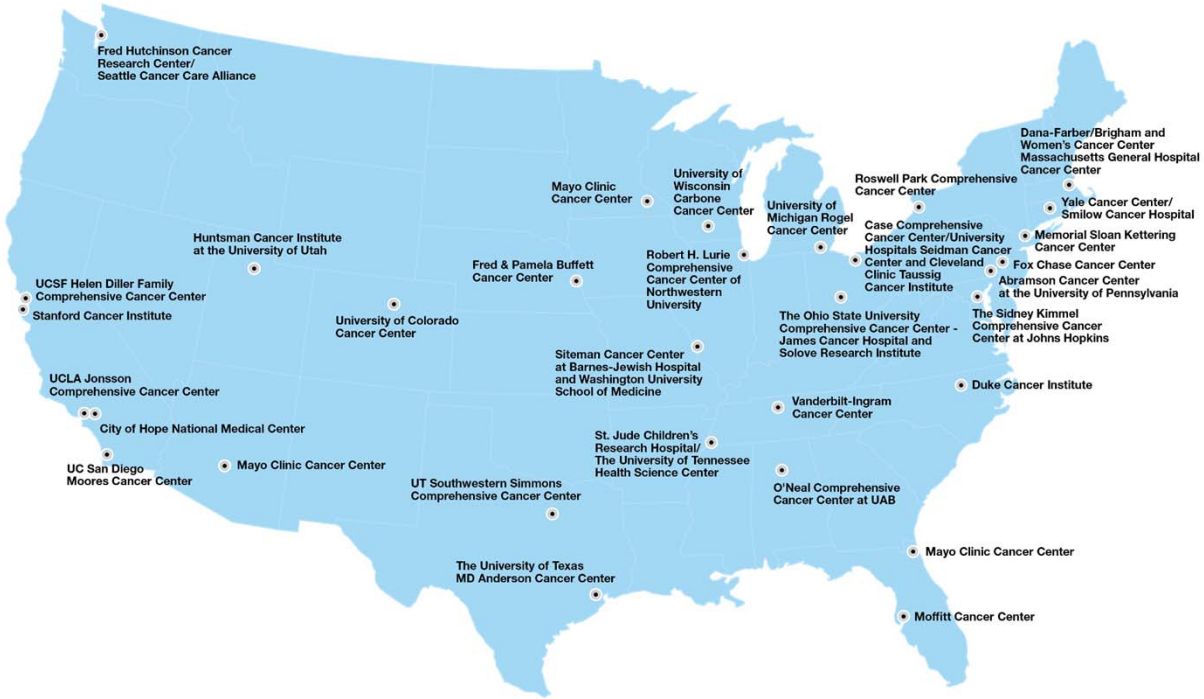

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