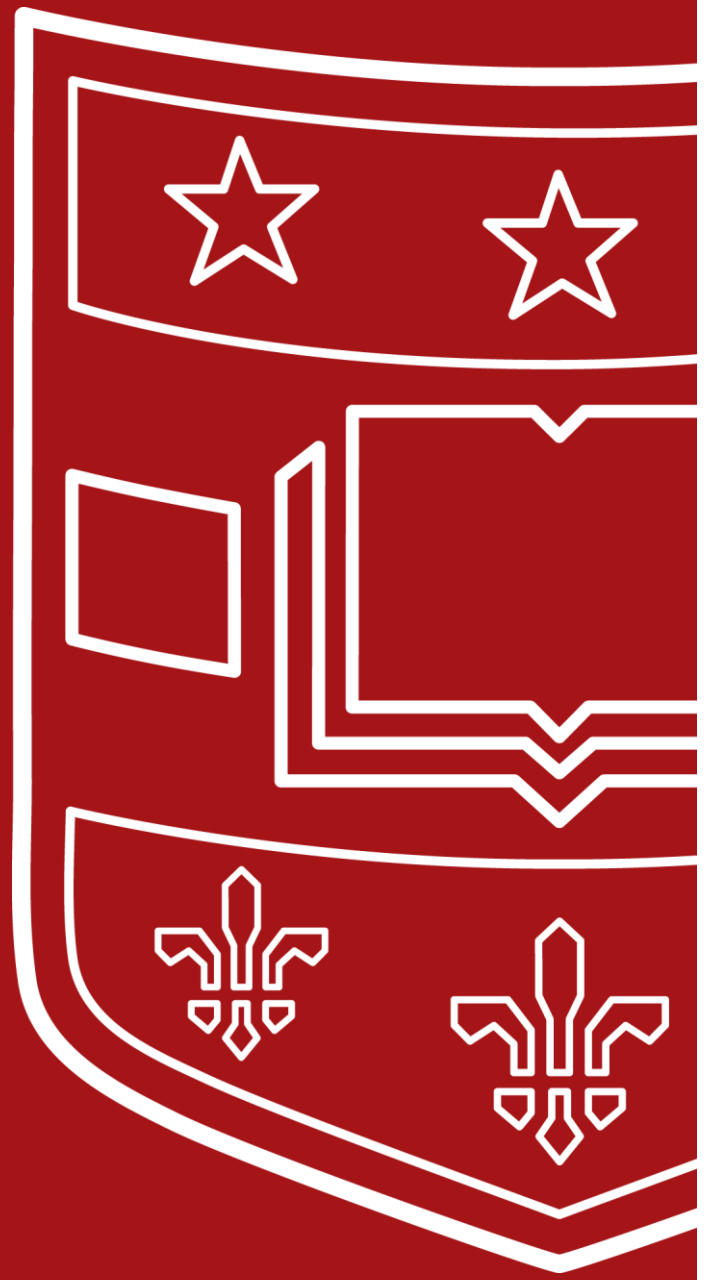
Whats New in Vascular Anomalies

Ogden Surgical-Medical Society
May 19, 2022

Bryan Sisk, Pediatric Hematology-Oncology

Katherine King, Genetics
Maithilee Menezes, Otolaryngology
Ali Mian, Neuroradiology
Alexander Ushinsky, Interventional Radiology
Leo Shmuylovich, Dermatology

Washington University in St. Louis



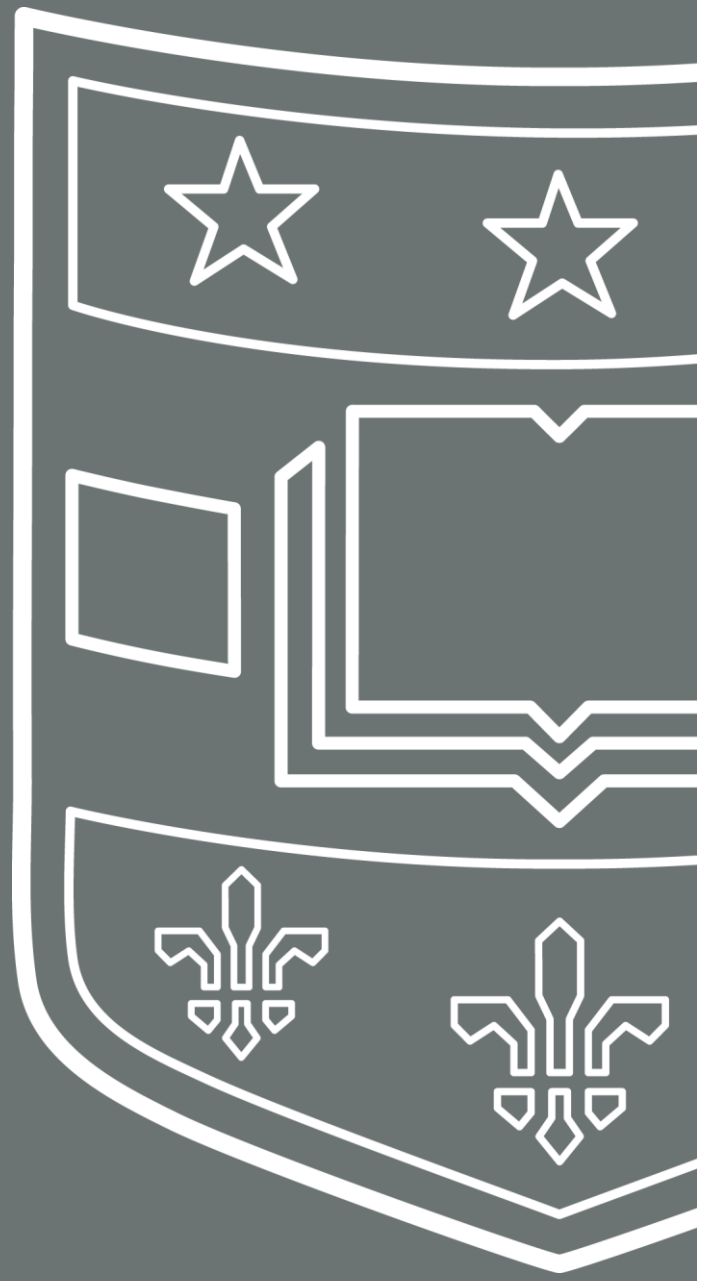
Objectives:

- Brief overview of vascular anomalies
- Genetics
- Targeted medical therapies

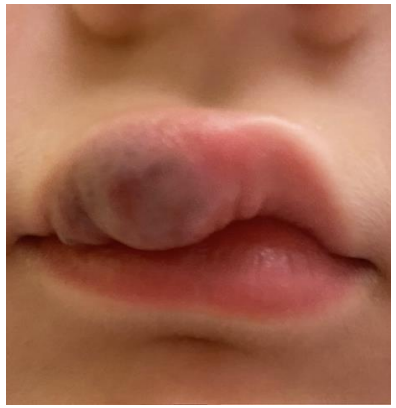
Key Takeaway Message

Consider referral to multidisciplinary vascular anomalies team for evaluation and treatment of complicated vascular malformations.

Brief Overview

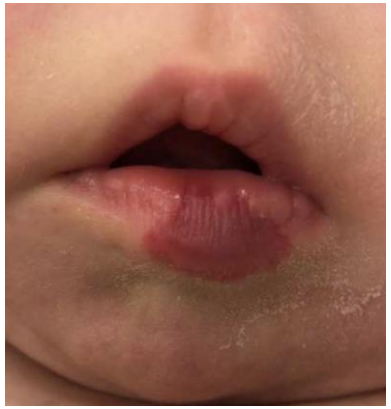


Vascular anomalies: A spectrum

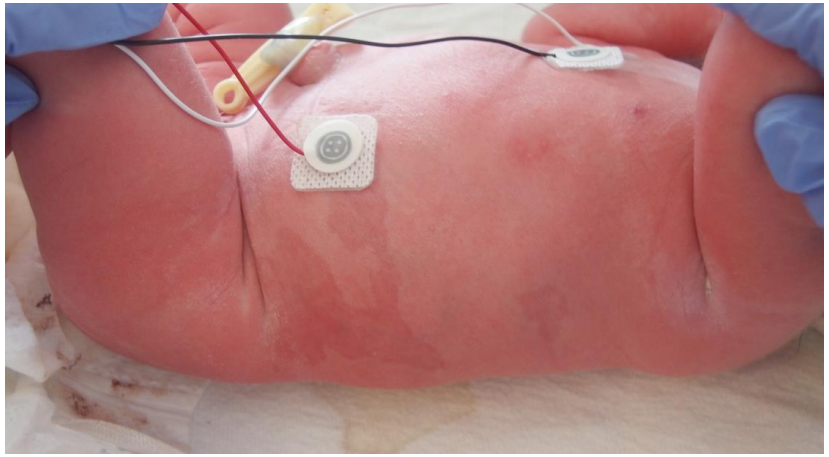


Arteriovenous malformation (*RASA1*)

Venous malformation



Capillary malformation (*PIK3CA*)



Capillary malformation (*AKT1*)

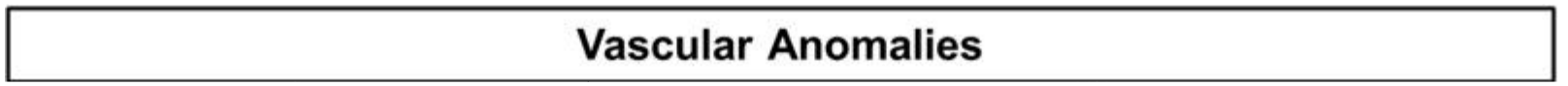
Capillary malformation (*PIK3CA*)

Capillary malformation (*GNAQ*)

Adapted from Leo Shmuylovich

Vascular anomalies:

- Definition:
  - Vascular anomaly: Spectrum of lesions of vascular tissue
  - Vascular tumor: Endothelial cell hyperproliferation
    - Often not present at birth
  - Vascular malformation: Defects in vessel formation
    - Usually present at birth



Treatment requires collaboration of a multidisciplinary team

mul·ti·dis·ci·pli·nar·y

/ˌməltēˈdisəpləˌnerē, ˌməltīˈdisəpləˌnerē/

adjective

combining or involving several academic disciplines or professional specializations in an approach to a topic or problem.

SLCH VAC

Otolaryngology
Dermatology
Hematology/Oncology
Genetics
Interventional Radiology
Plastic Surgery
Radiology
Surgery

***Inpatient and Outpatient**

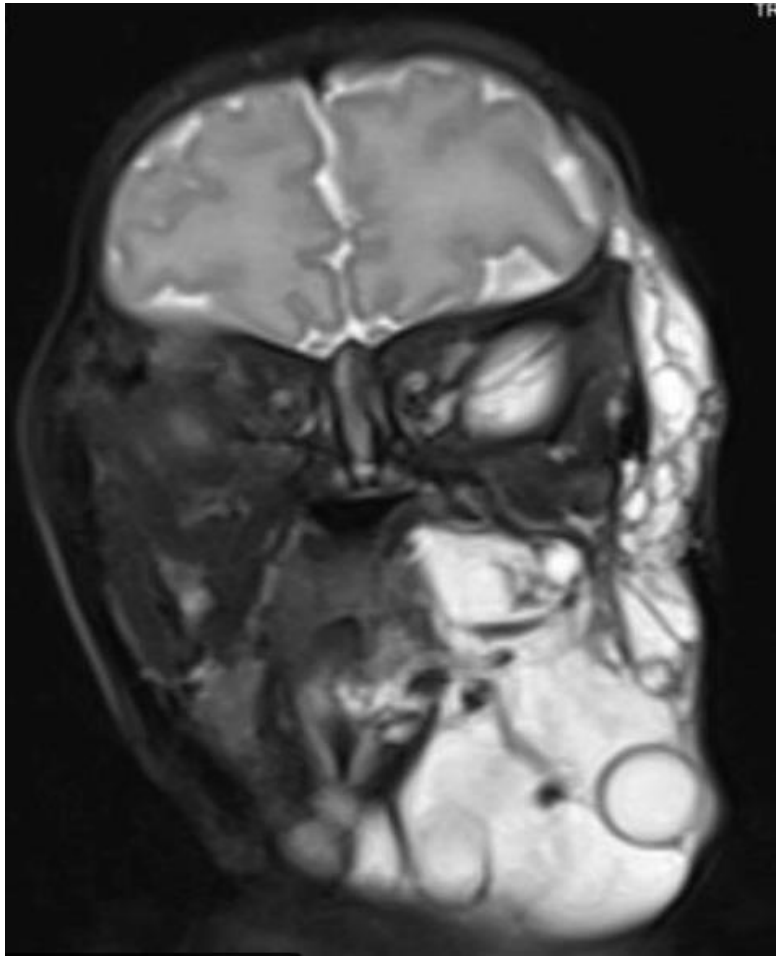
***Medical home**

Vascular anomalies team: Patients

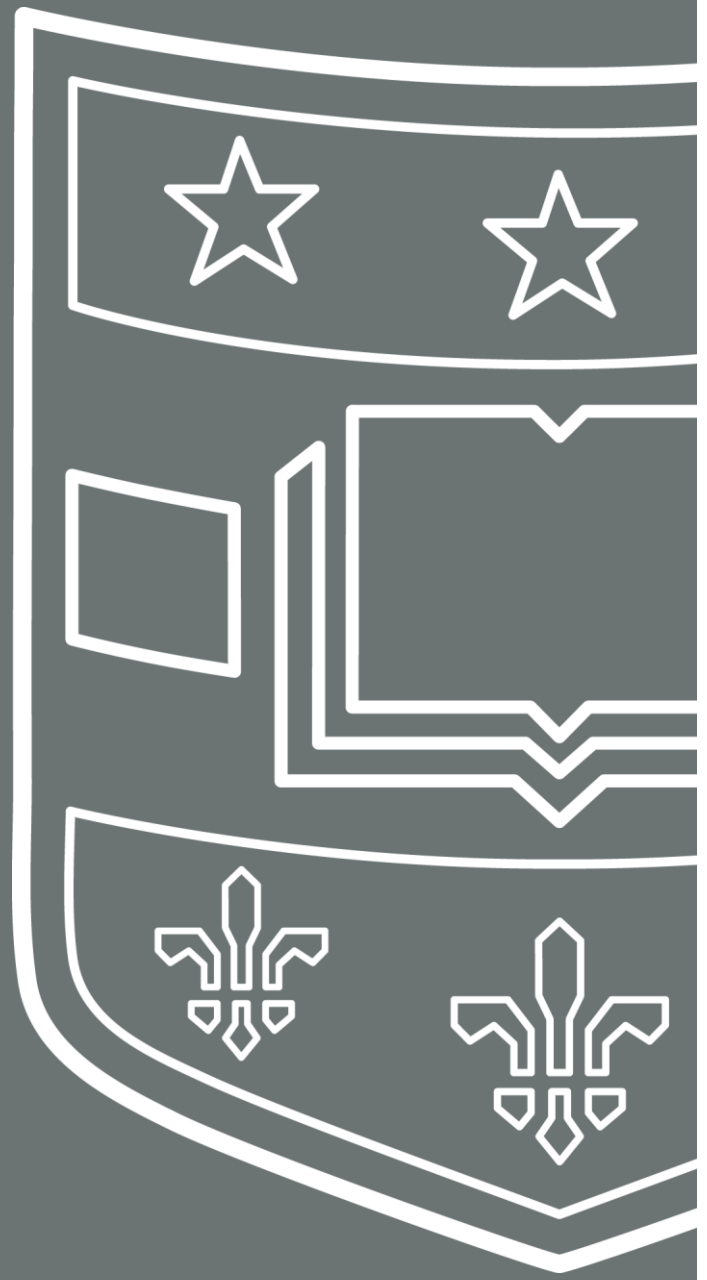
- Presentations:
  - Isolated head and neck
  - Single limb
  - Diffuse
- Common complications:
  - “Flare”
  - Overgrowth
  - Chronic pain
  - Lack of medical home

Vascular anomalies team: Patients

- Work-up / Management:
  - Imaging
    - Ultrasound
    - MRI
  - Intervention
    - Compression
    - Lymphatic massage
    - Surgery
    - Sclerotherapy
    - Medications
  - Genetic testing

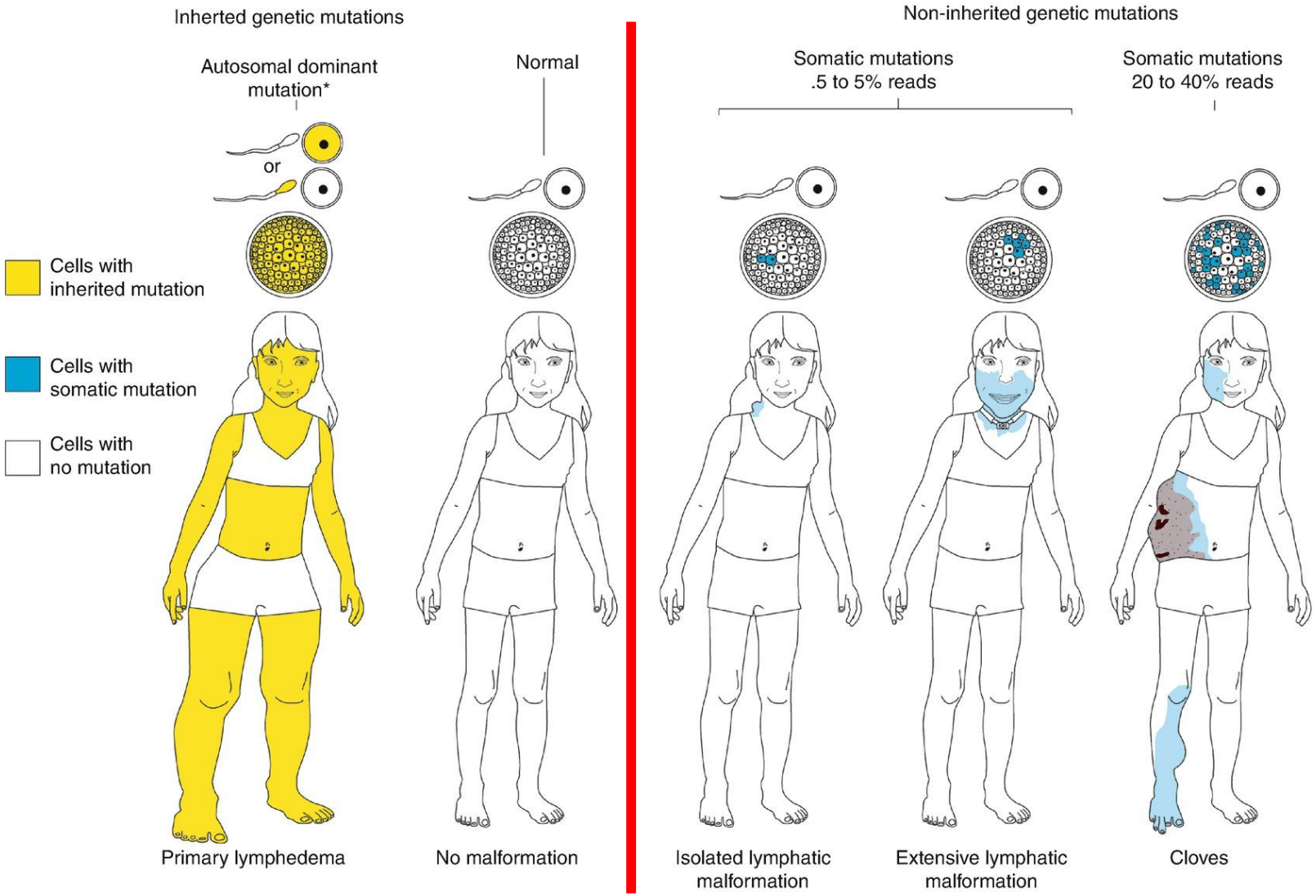


Genetics of Vascular Anomalies



Washington University in St. Louis

Vascular anomalies: Mosaicism



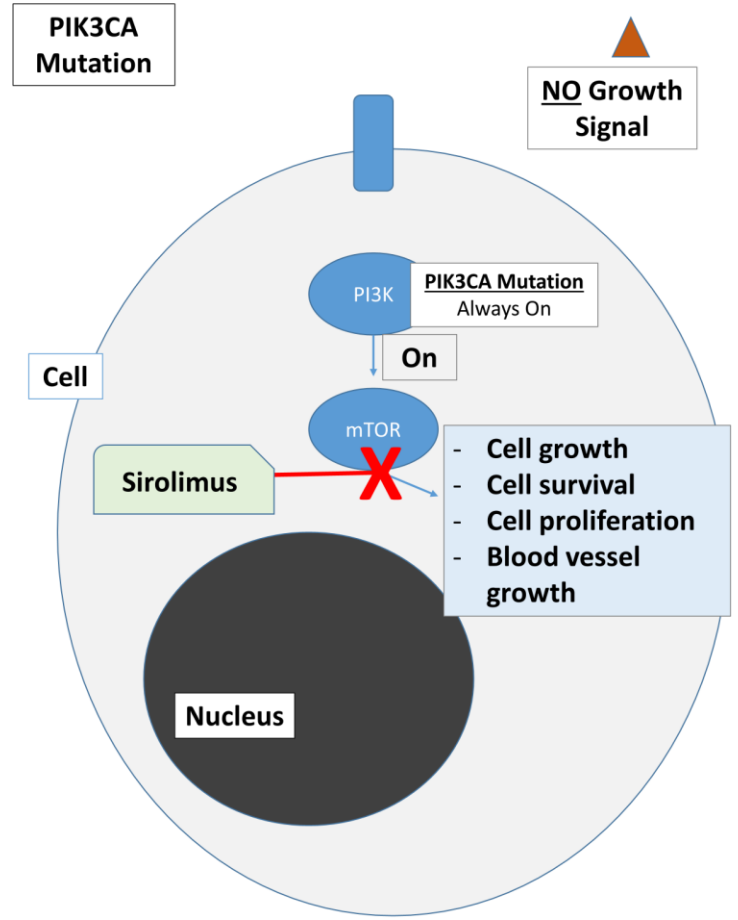
Perkins, 2018

Genetics has become an important part of diagnosis and treatment

"Proliferation pathway"

Role in cell cycle regulation, proliferation, migration

Activated when a growth factor binds to receptor tyrosine kinase



Timeline:

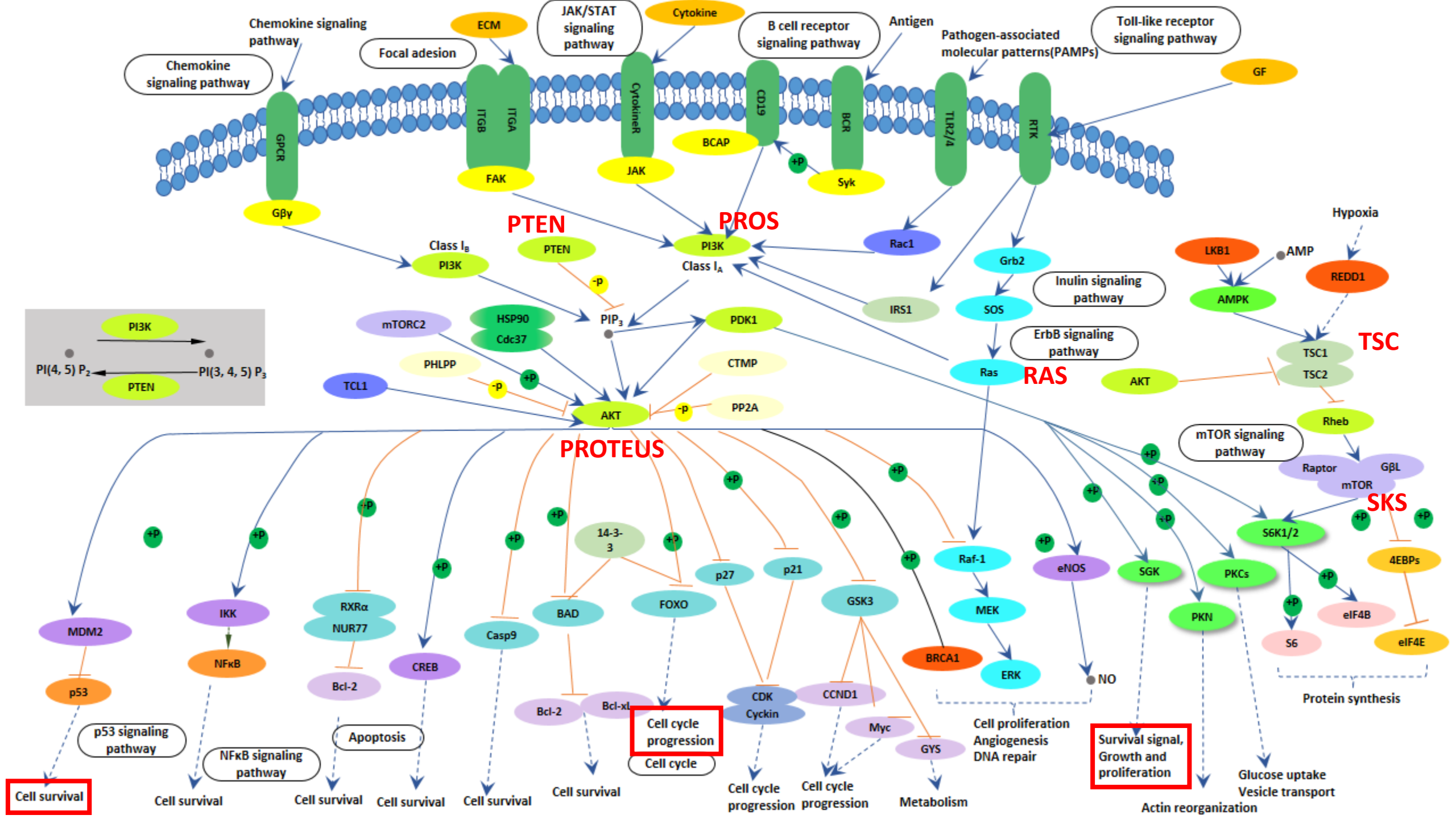
1980s:
Phosphoinositide 3-kinase (PI3K) is important for cellular growth

1994:
MTOR identified
Volinia et al. 1994:
PIK3CA maps to 3q26.3
Li et al. 1997:
PTEN on 10q23, candidate tumor suppressor
Liaw et al. 1997:
PTEN germline variants in Cowden syndrome

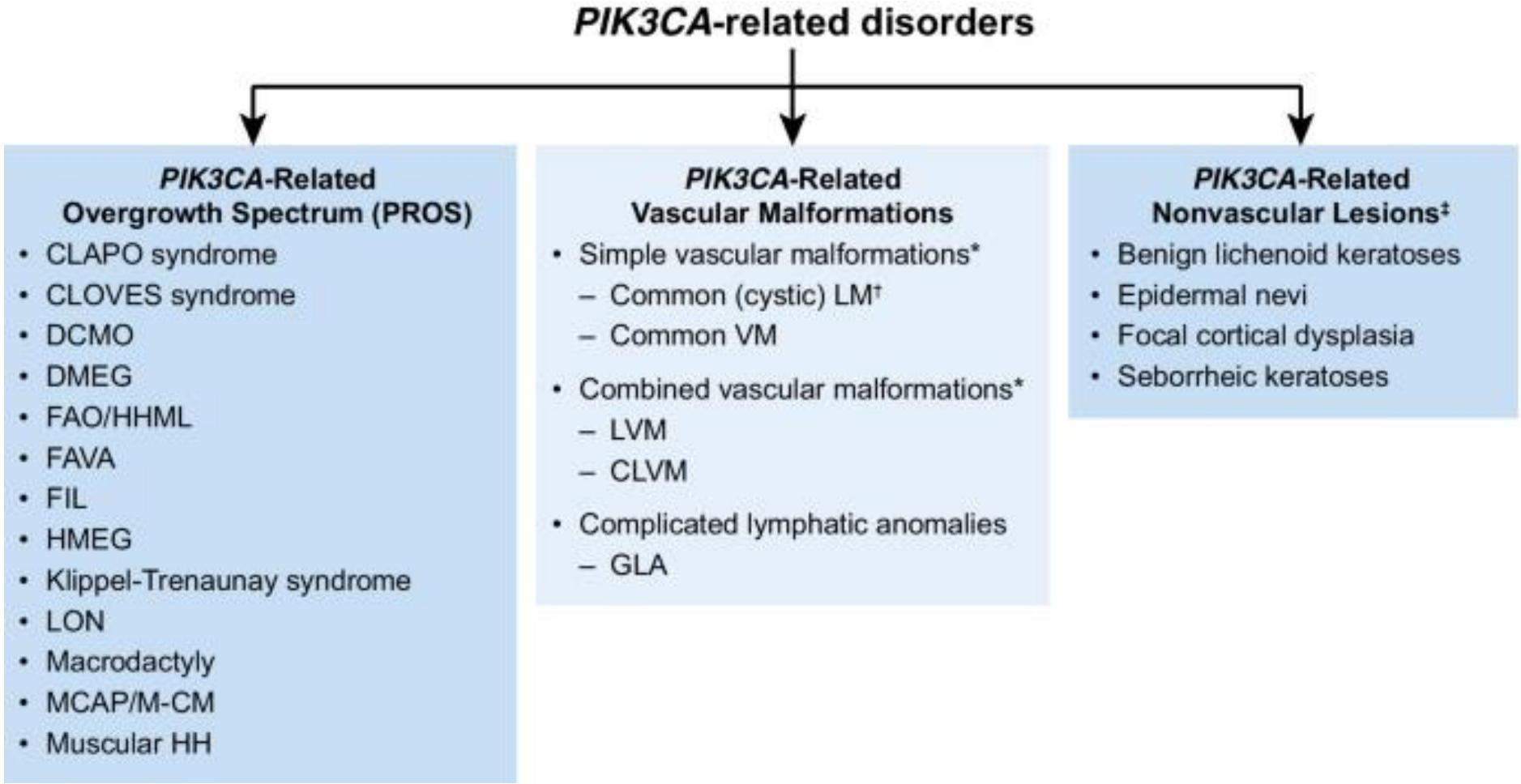
Samuels et al. 2004:
PI3K genes (*PIK3CA* hotspot) activating mutations in human tumors

Lindhurst et al. 2011:
Mosaic activating *AKT1* variant associated with Proteus syndrome
Lindhurst et al. 2012:
Mosaic overgrowth disorders from *PIK3CA*

Keppler-Noreuil et al. 2015:
PIK3CA-related overgrowth spectrum (PROS) criteria

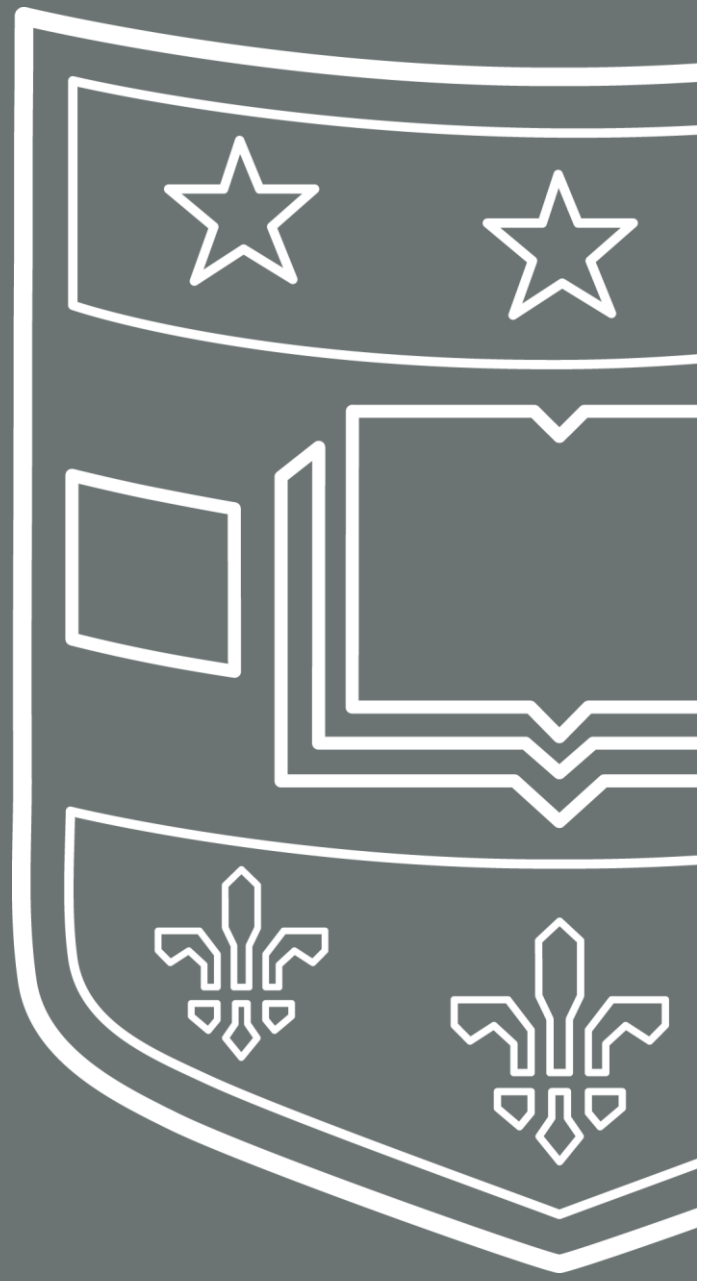

Chemokine signaling pathway
Chemokine signaling pathway
ECM
Focal adesion
JAK/STAT signaling pathway
Cytokine
B cell receptor signaling pathway
Antigen
Pathogen-associated molecular patterns(PAMPs)
Toll-like receptor signaling pathway
GF
GPCR
ITGB
ITGA
CytokineR
CD19
BCR
TLR2/4
RTK
FAK
JAK
BCAP
Syk
+P
Gβγ
PTEN
PROS
Class I_B
PI3K
PTEN
PI3K
Class I_A
Rac1
Grb2
Hypoxia
LKB1
AMP
REDD1
AMPK
Inulin signaling pathway
IRS1
SOS
ErbB signaling pathway
TSC
TSC1
TSC2
Ras
RAS
AKT
PI3K
PI(4, 5) P_2
PI(3, 4, 5) P_3
PTEN
mTORC2
HSP90
Cdc37
PHLPP
TCL1
PIP_3
PDK1
CTMP
PP2A
AKT
PROTEUS
Rheb
mTOR signaling pathway
Raptor
GβL
mTOR
SKS
S6K1/2
4EBPs
eIF4B
eIF4E
S6
Protein synthesis
Raf-1
MEK
ERK
eNOS
NO
SGK
PKCs
PKN
MDM2
p53
IKK
NFκB
RXRα
NUR77
Bcl-2
CREB
Casp9
14-3-3
BAD
Bcl-2
Bcl-xL
FOXO
p27
p21
CDK
Cyckin
CCND1
Myc
GSK3
GYS
BRCA1
p53 signaling pathway
NFκB signaling pathway
Apoptosis
Cell cycle progression
Cell cycle
Cell proliferation
Angiogenesis
DNA repair
Survival signal, Growth and proliferation
Glucose uptake
Vesicle transport
Actin reorganization
Metabolism
Cell survival
Cell survival
Cell survival
Cell survival
Cell survival
Cell survival
Cell cycle progression
Cell cycle progression

PIK3CA-related disorders: Canaud et al. 2021



Canaud et al. 2021

Management Considerations



Treatment of lesions driven by functional impairment, symptoms, and quality of life

Functional Impairment

Airway compromise

Inability to swallow/ eat

Vision Impairment

Consumption of platelets

Coagulopathy

Impingement of other vital structures

Chylous effusions

Symptoms/QOL

Chronic pain

Swelling

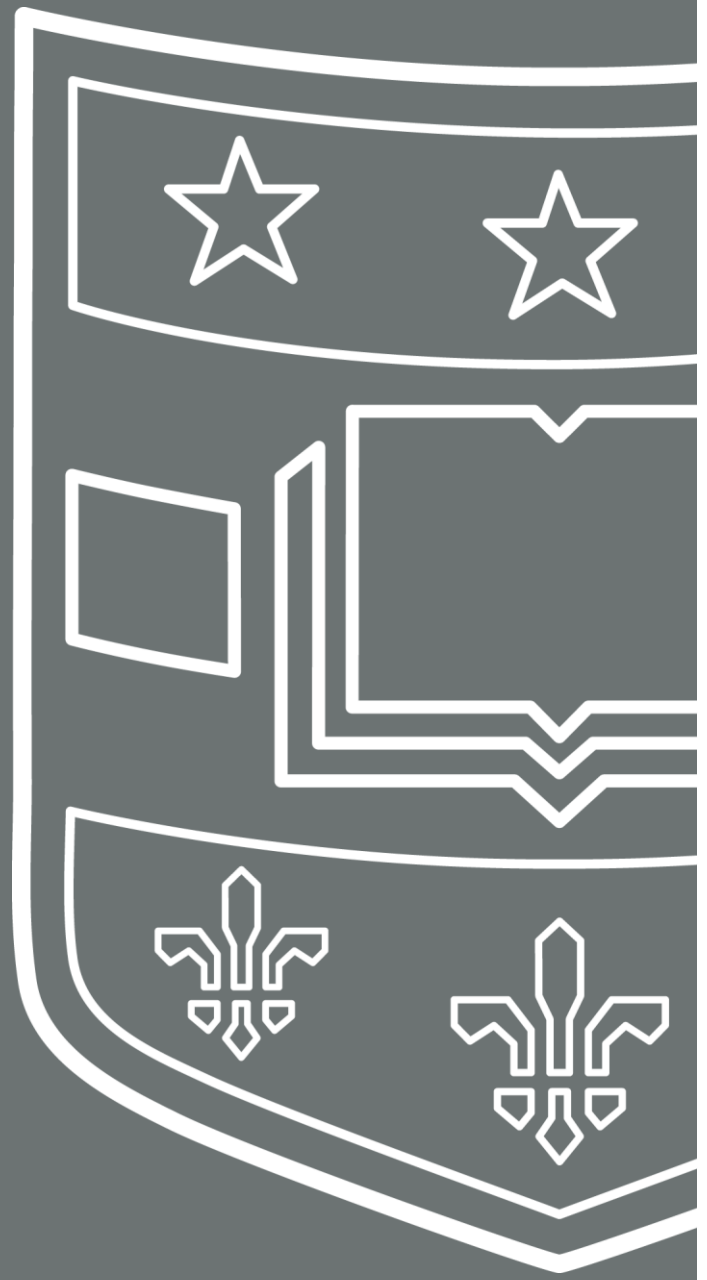
Frequent flares

Psychological distress

Management:

- Conservative:
  - Observation
  - Compression
  - Lymphatic massage
- Invasive:
  - Sclerotherapy
  - Surgery
- Medical:
  - Targeted inhibitors
  - Vincristine
  - Interferon
  - Steroids/Antibiotics
- Monitoring
  - Imaging
  - Long-term follow-up

Targeted Therapeutics



How one person made a difference

Starting sirolimus therapy

21 months on

18 months off

Recent

ISSVA 2010

*Slide courtesy of Denise Adams

Pediatr Blood Cancer 2011;57:1018–1024

Sirolimus for the Treatment of Complicated Vascular Anomalies in Children

Adrienne M. Hammill, MD, PhD,[1,2]* MarySue Wentzel, RN,[1] Anita Gupta, MD,[1,3] Stephen Nelson, MD,[4] Anne Lucky, MD,[1,5] Ravi Elluru, MD, PhD,[1,6] Roshni Dasgupta, MD,[1,7] Richard G. Azizkhan, MD,[1,7] and Denise M. Adams, MD[1,2]

6 patients with complicated, life-threatening vascular anomalies

Sirolimus

All responded to therapy

Treatment Options: Targeted Inhibitors - Sirolimus

Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies

Denise M. Adams, MD,[a,b] Cameron C. Trenor III, MD, PhD,[c] Adrienne M. Hammill, MD, PhD,[a,b] Alexander A. Vinks, PhD,[a,b] Manish N. Patel, DO,[a,b] Gulraiz Chaudry, MBChB,[c] Mary Sue Wentzel, MSN,[a] Paula S. Mobberley-Schuman, MS,[a] Lisa M. Campbell, MS,[a] Christine Brookbank, MEd,[a] Anita Gupta, MD,[a,b] Carol Chute, APRN,[a] Jennifer Eile, CPNP,[c] Jesse McKenna, MPH,[c] Arnold C. Merrow, MD,[a,b] Lin Fei, PhD,[a] Lindsey Hornung, MS,[a] Michael Seid, PhD,[a] A. Roshni Dasgupta, MD,[a,b] Belinda H. Dickie, MD,[a,b] Ravindhra G. Elluru, MD,[d] Anne W. Lucky, MD,[a] Brian Weiss, MD,[a,b] Richard G. Azizkhan, MD[e]

61 patients with complicated vascular anomalies

Sirolimus for 1 year

47 partial responses

3 stable disease

7 progressive disease

Adams, et al. *Pediatrics* 2016

Most patients tolerate Sirolimus, but not everyone

113 patients with vascular malformations

DOI: 10.1002/pbc.28936

HEMATOLOGY: RESEARCH ARTICLE

Pediatric Blood & Cancer | aspho | WILEY

Severe adverse events during sirolimus "off-label" therapy for vascular anomalies

Jochen Rössler[1,2,3,4] | Eulalia Baselga[5] | Victoria Davila[5] | Veronica Celis[6] | Andrea Diociaiuti[3,7] | Maya El Hachem[3,7] | Sandrine Mestre[4] | Dario Haeberli[8] | Aram Prokop[9] | Christof Hanke[10] | Wolfgang Loichinger[11] | Isabelle Quéré[4] | Iris Baumgartner[8] | Charlotte M. Niemeyer[2,3] | Friedrich G. Kapp[2,3]

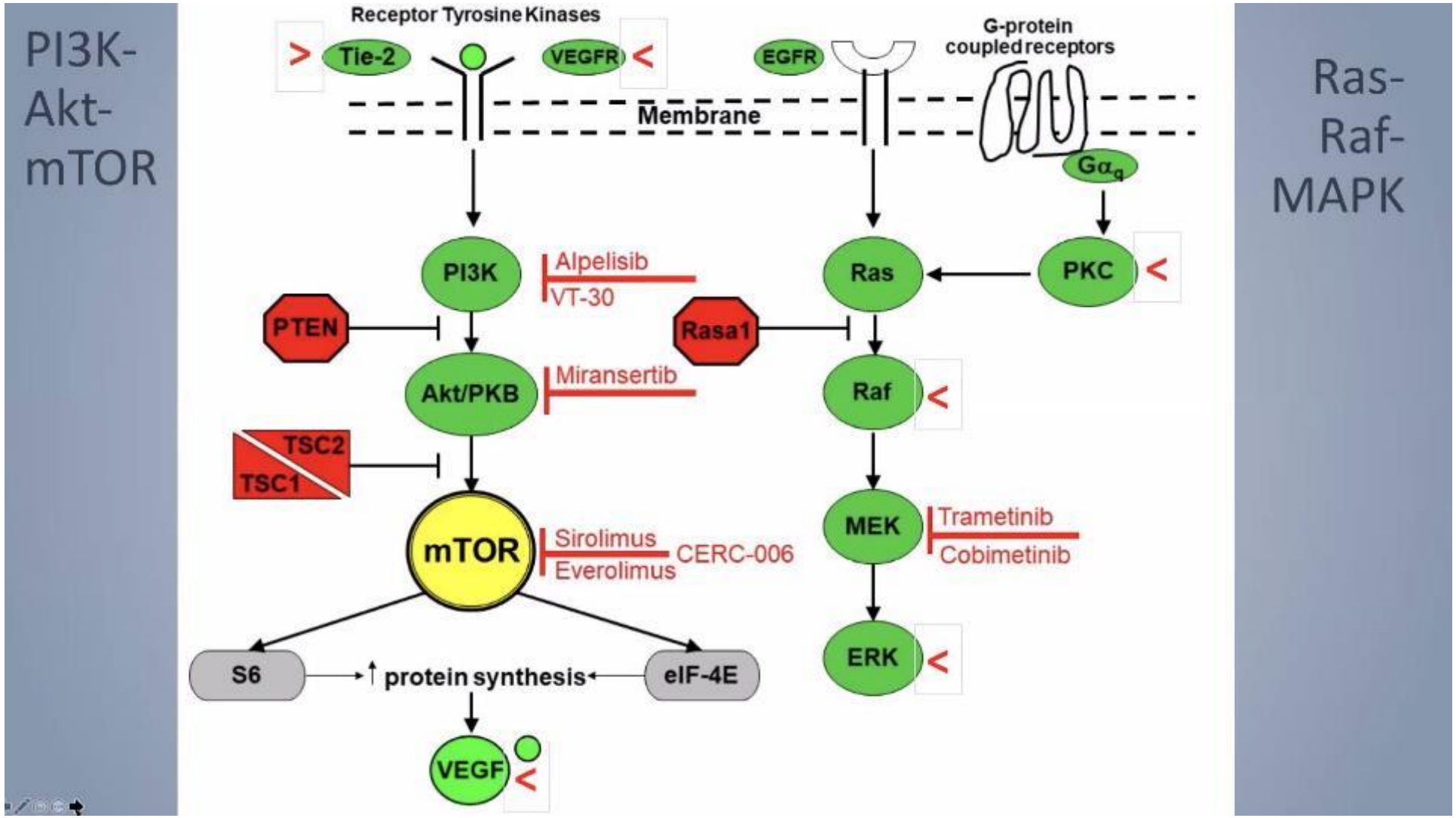
Sirolimus →

14 patients with serious adverse events

- 8 viral pneumonia
- 1 pneumococcal pneumonia
- 3 foreign body infections (catheter, bone implant)
- 1 thrombophlebitis
- 2 diarrhea

Rossler, et al. PBC, 2021

Future directions: Targeted inhibitors



Ongoing clinical trials:

Drug	Target	Trial Name	Eligibility	Study Design	Status
Miransertib	Akt1/2/3		Age: >2yo	Phase 2	Closed to Enrollment
Alpelisib	PI3Kα				
VT-30	PIK3				
Trametinib	MEK1/2				
Cobimetinib	MEK1				
CERC-006 AVTX-006	mTORC1/2		Age: 18-31yo Dx: Complicated Lymphatic Malformations	Phase 1b Proof of concept study Multiple sites	Enrolling

Consortium of iNvestigators of Vascular AnomalieS (CaNVAS)

The Consortium of iNvestigators of Vascular AnomalieS (CaNVAS) is a multi-institutional research consortium founded by a group of Pediatric Hematologist/Oncologists and patient advocacy groups to address the rare nature of vascular anomalies and the paucity of prospective multi-centered research in this field, particularly as it relates to novel therapies and outcome studies.

Take-aways:

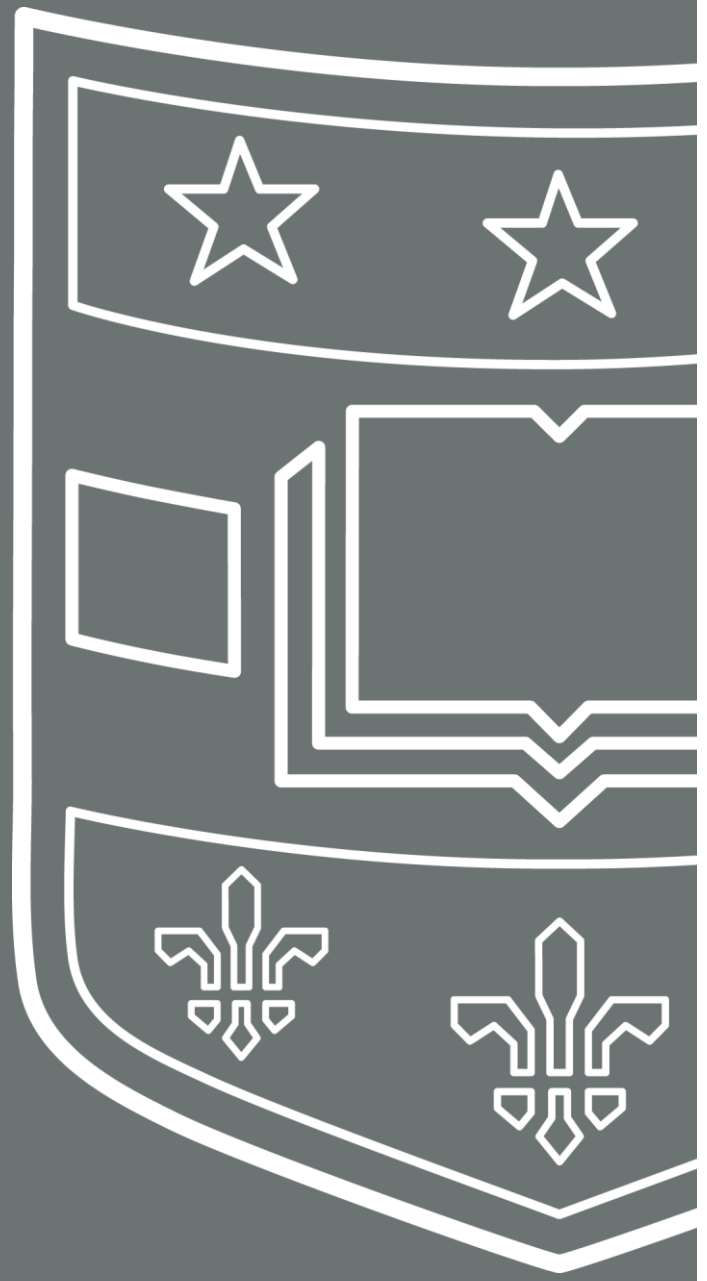
- Field of vascular anomalies is expanding with clinical trials and new treatments.
- Patients have unique diagnostic and management considerations.
- Need for multidisciplinary approach. Consider referrals to multidisciplinary teams (often at children’s hospitals).

Questions?

Please contact me if you need help finding a multidisciplinary vascular anomalies team!

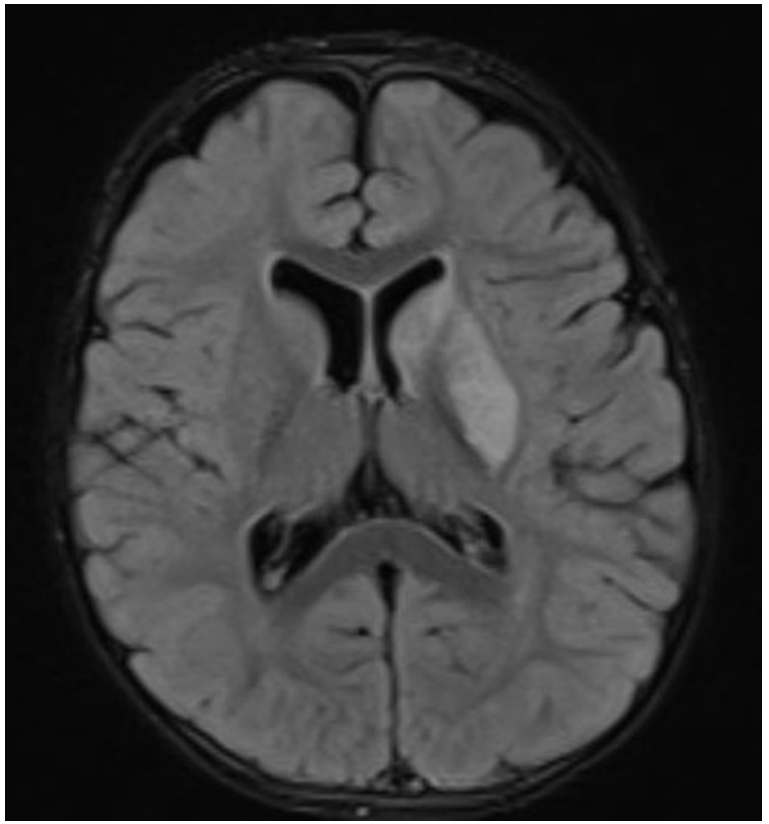
Bryan Sisk, MD, MSCI
siskb@wustl.edu
Twitter @sisk_md

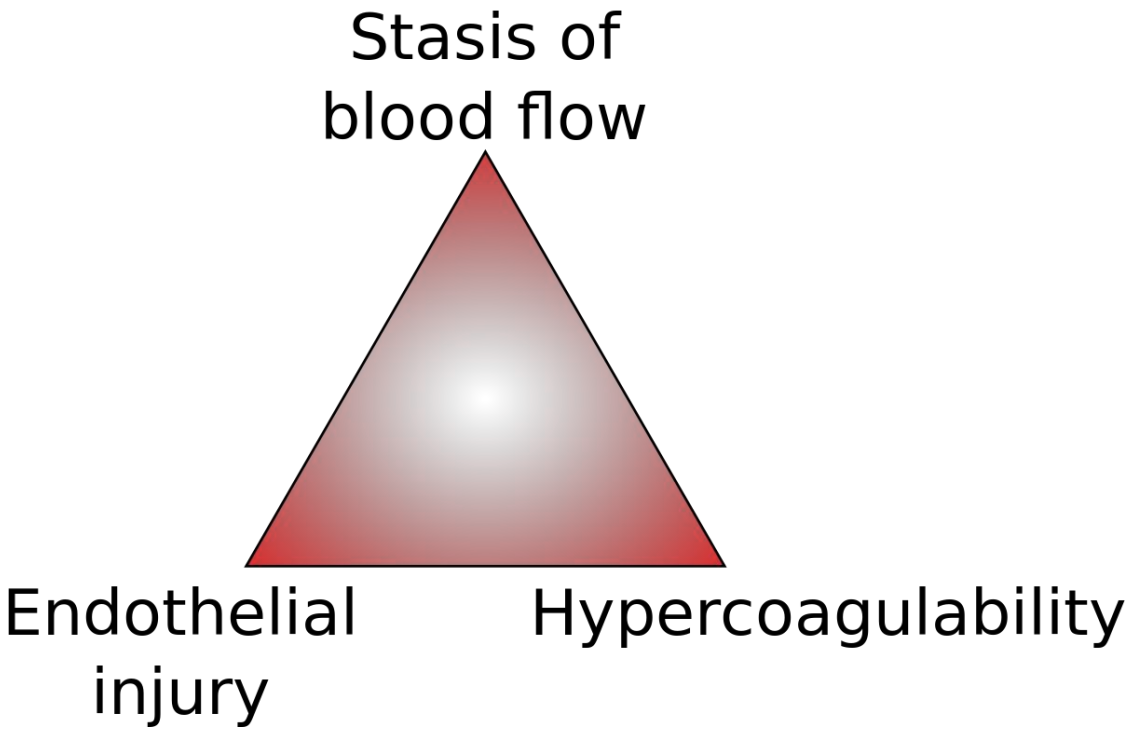
Managing Complications



Management: Thrombosis Risk

- 18 month old girl with PROS
- After ASD repair, corpus striatum infarct
- Spastic hemiplegia

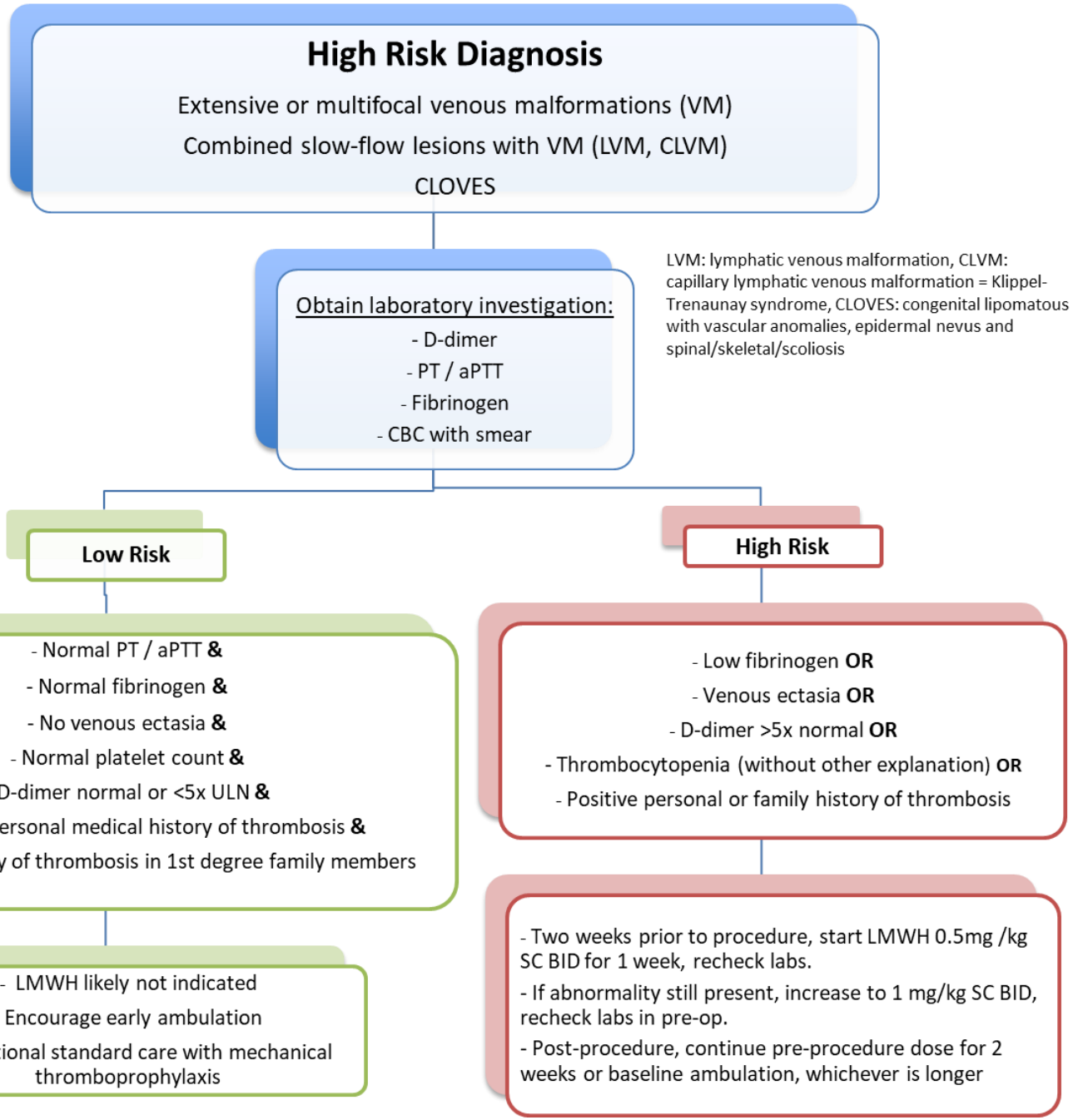




Abnormal endothelium lining (structural and functional)

Abnormal size and direction of the vessels and blood flow

Localized intravascular coagulopathy (LIC)


High Risk Diagnosis
Extensive or multifocal venous malformations (VM)
Combined slow-flow lesions with VM (LVM, CLVM)
CLOVES
Obtain laboratory investigation:
- D-dimer
- PT / aPTT
- Fibrinogen
- CBC with smear
LVM: lymphatic venous malformation, CLVM: capillary lymphatic venous malformation = Klippel-Trenaunay syndrome, CLOVES: congenital lipomatous with vascular anomalies, epidermal nevus and spinal/skeletal/scoliosis
Low Risk
- Normal PT / aPTT &
- Normal fibrinogen &
- No venous ectasia &
- Normal platelet count &
- D-dimer normal or <5x ULN &
- Negative personal medical history of thrombosis &
- No family history of thrombosis in 1st degree family members
- LMWH likely not indicated
- Encourage early ambulation
- Institutional standard care with mechanical thromboprophylaxis
High Risk
- Low fibrinogen OR
- Venous ectasia OR
- D-dimer >5x normal OR
- Thrombocytopenia (without other explanation) OR
- Positive personal or family history of thrombosis
- Two weeks prior to procedure, start LMWH 0.5mg /kg SC BID for 1 week, recheck labs.
- If abnormality still present, increase to 1 mg/kg SC BID, recheck labs in pre-op.
- Post-procedure, continue pre-procedure dose for 2 weeks or baseline ambulation, whichever is longer