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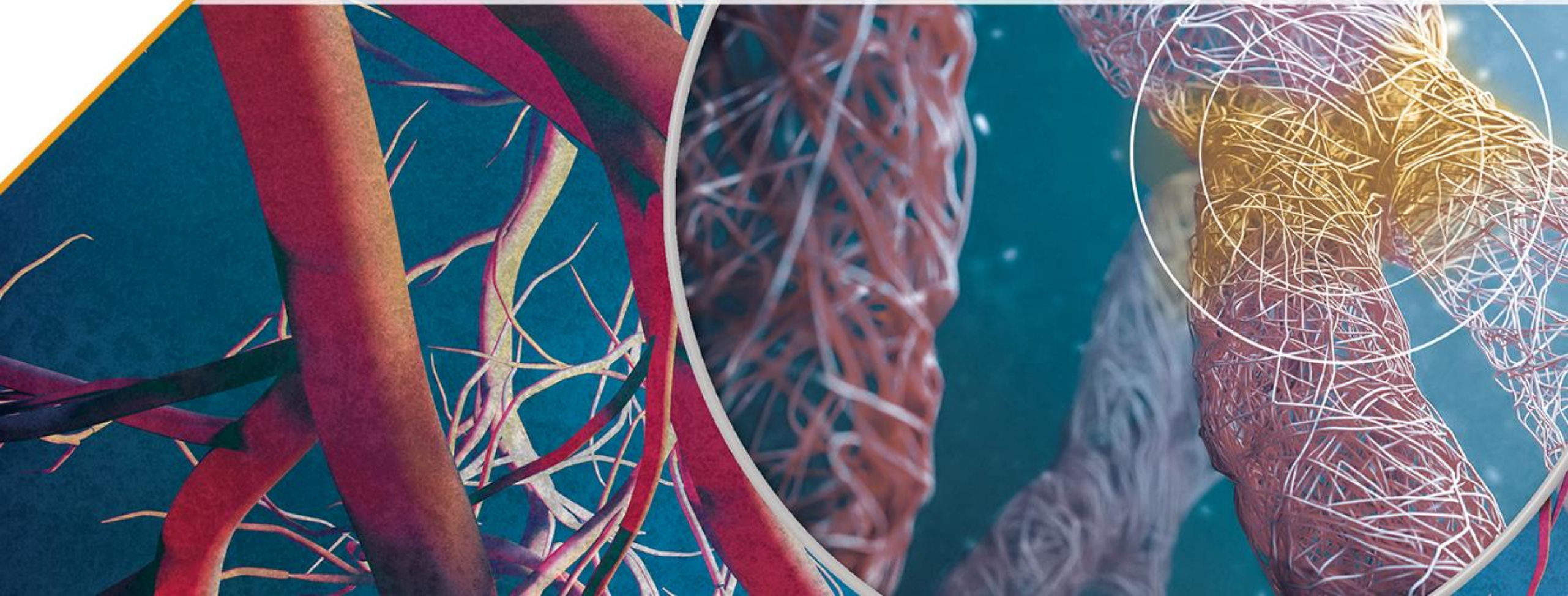
Evolving Perspectives in PIK3CA-related Overgrowth Spectrum (PROS) Diagnosis and Treatment



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Disclosure of Conflicts of Interest

Julie Blatt, MD

- Reported a financial interest/relationship or affiliation in the form of *Contracted research*: Novartis Pharmaceuticals Corp.

Taizo Nakano, MD

- Reported a financial interest/relationship or affiliation in the form of *Consultant*: Novartis Pharmaceuticals Corp. *Advisory board/consulting*: Swedish Orphan Biovitrum (Sobi).

Learning Objectives

Upon completion of this activity, participants should be better able to:

- Summarize the role of the PI3K/AKT/mTOR pathway in cell proliferation that result in rare and complex disorders, and improve awareness of the epidemiology, burden, and need for timely referral of patients with PROS
- Outline difficulties related to obtaining a PROS diagnosis and the psychological and quality of life challenges this often creates for patients and families
- Compare traditional therapeutic approaches for PROS, including treatment goals, with the objectives of current clinical trials assessing the efficacy and safety of novel agents
- Evaluate the clinical efficacy and safety data of current and past clinical trials, review best practices, and improve understanding of how to incorporate emerging treatment options that address the root causes of PROS

The International Society for the Study of Vascular Anomalies Classification System

ISSVA classification for vascular anomalies ©

(Approved at the 20th ISSVA Workshop, Melbourne, April 2014, last revision May 2018)

This classification is intended to evolve as our understanding of the biology and genetics of vascular malformations and tumors continues to grow

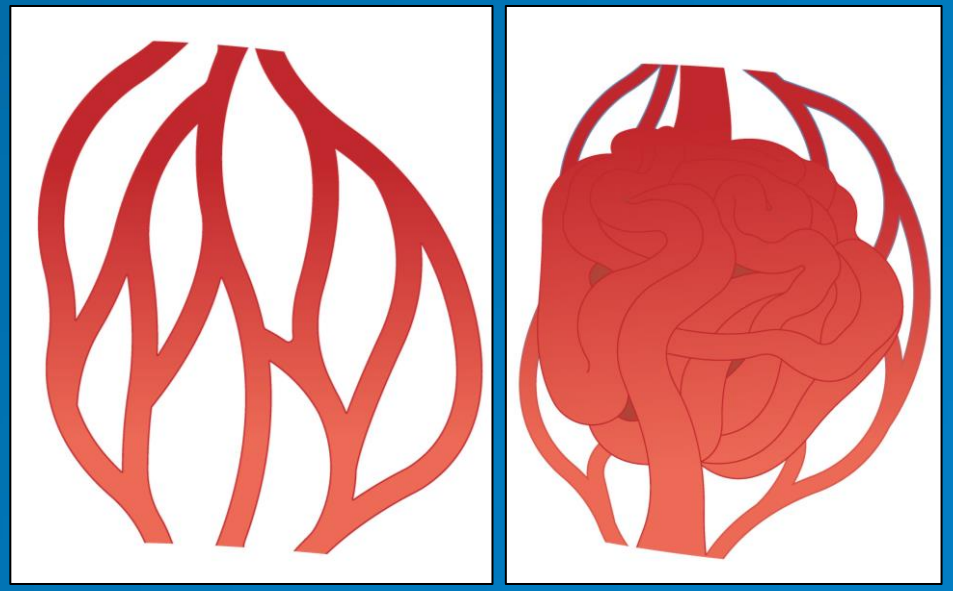
Overview table

Vascular anomalies				
Vascular tumors	**Vascular malformations**			
	Simple	**Combined •**	**of major named vessels**	**associated with other anomalies**
Benign Locally aggressive or borderline Malignant	Capillary malformations Lymphatic malformations Venous malformations Arteriovenous malformations* Arteriovenous fistula*	CVM, CLM LVM, CLVM CAVM* CLAVM* others	See details	See list

• defined as two or more vascular malformations found in one lesion
* high-flow lesions

A list of causal genes and related vascular anomalies is available in Appendix 2

The tumor or malformation nature or precise classification of some lesions is still unclear. These lesions appear in a separate provisional list.



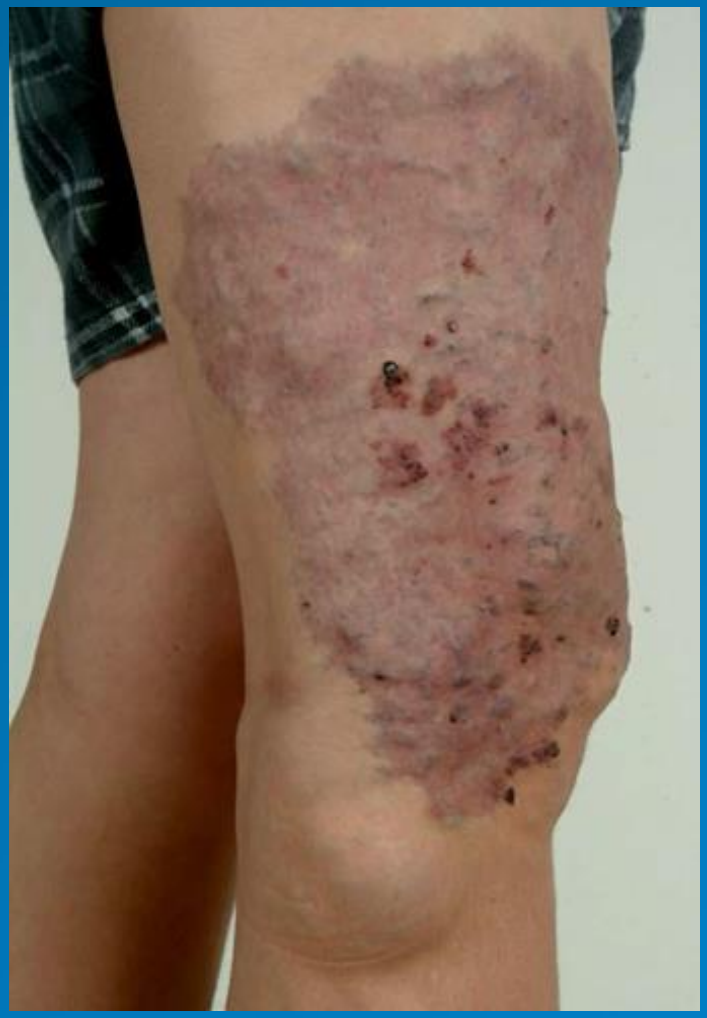
Normal | Malformation

CVM, capillary venous malformation; CLM, capillary lymphatic malformation; LVM, lymphatic venous malformation; CLVM, capillary lymphatic venous malformation; CAVM, capillary arteriovenous malformation; CLAVM, capillary lymphatic arteriovenous malformation.

ISSVA Classification of Vascular Anomalies ©2018 International Society for the Study of Vascular Anomalies Available at issva.org/classification. Accessed July 12, 2022.

Klippel Trenaunay Syndrome: CLVM

- Hemihypertrophy (overgrowth)
- Capillary malformation
- Vascular malformation
  - Venous malformation
  - Lymphatic malformation



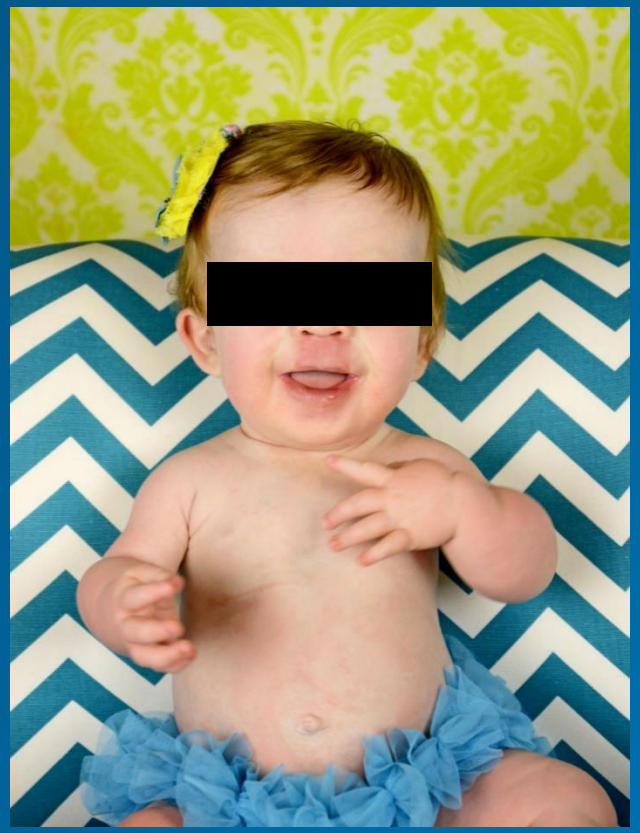
CLVM, capillary lymphatic venous malformation.

CLOVES Syndrome

- Congenital
- Lipomatous
- Overgrowth
- Vascular malformations
- Epidermoid nevi
- Scoliosis/skeletal/spinal problems

CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal abnormatlities.

MCAP Syndrome



- Megalencephaly
- Capillary malformation

MCAP, megalencephaly-capillary malformation polymicrogyria.

PIK3CA-Related Overgrowth Syndromes

- CLOVES
- CLAPO
- DCMO
- DMEG
- FAO/HHML
- FAVA
- FIL
- HH
- HMEG
- KTS
- LON
- Macrodactyly
- MCAP/M-CM

CLAPO: capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry and partial/generalized overgrowth; CLOVES: congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal; CLVM: combined capillary-lymphatic-venous malformation; DCMO: diffuse capillary malformation with overgrowth; DMEG: dysplastic megalencephaly; FAO/HHML: fibroadipose hyperplasia or overgrowth/hemihyperplasia-multiple lipomatosis; FAVA: fibroadipose vascular anomaly; FIL: fibroadipose or facial infiltrating lipomatosis; GLA, generalized lymphatic anomaly; HH: hemihyperplasia; HMEG: hemimegalencephaly; LM, lymphatic malformation; LON: lipomatosis of nerve; LVM: combined lymphatic-venous malformation; MCAP: megalencephaly-capillary malformation; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; VM, venous malformation.

Modified from Canaud et al. *Orphanet J Rare Dis*. 2021;16:306.

PIK3CA–Related Vascular Malformations

- Simple vascular malformations: **LM, VM**
- Complicated lymphatic malformations: **LVM, CLVM**
- Complicated lymphatic anomalies: **GLA**

PIK3CA–Related Nonvascular Lesions

- Epidermal nevi
- Seborrheic keratoses
- Benign lichenoid keratosis
- Focal cortical dysplasia

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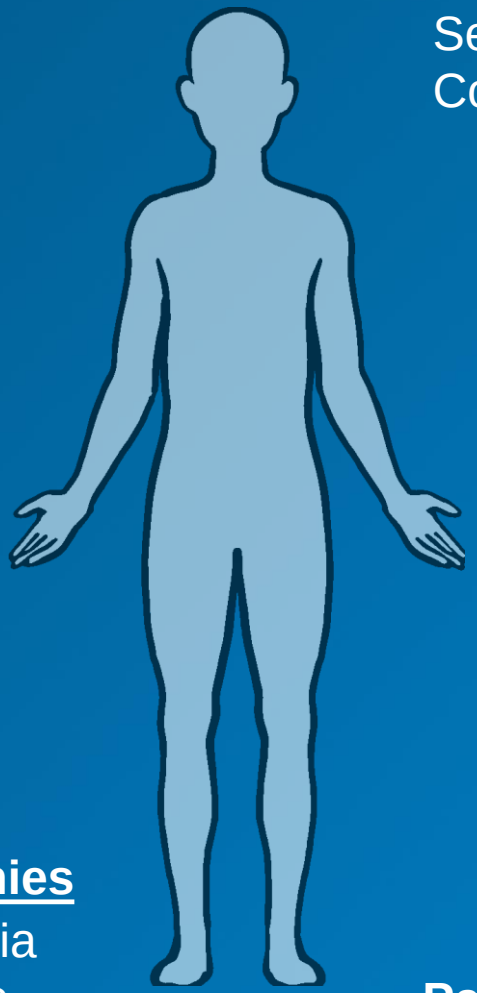
Complications of PROS

Psychological
- Anxiety
- Depression

Organ abnormalities
- Pulmonary
- GI
- Hepatic
- Renal
- Cardiac

Functional impairment
- Soft-tissue overgrowth
- Orthopedic
- Muscular
- Central and peripheral nervous system

Coagulopathies
- Thrombophilia
- Hemorrhagic



Neurodevelopmental
- Megalencephaly
- Seizures
- Cognitive changes

Cardiovascular
- Orthostatic
- Hypotension

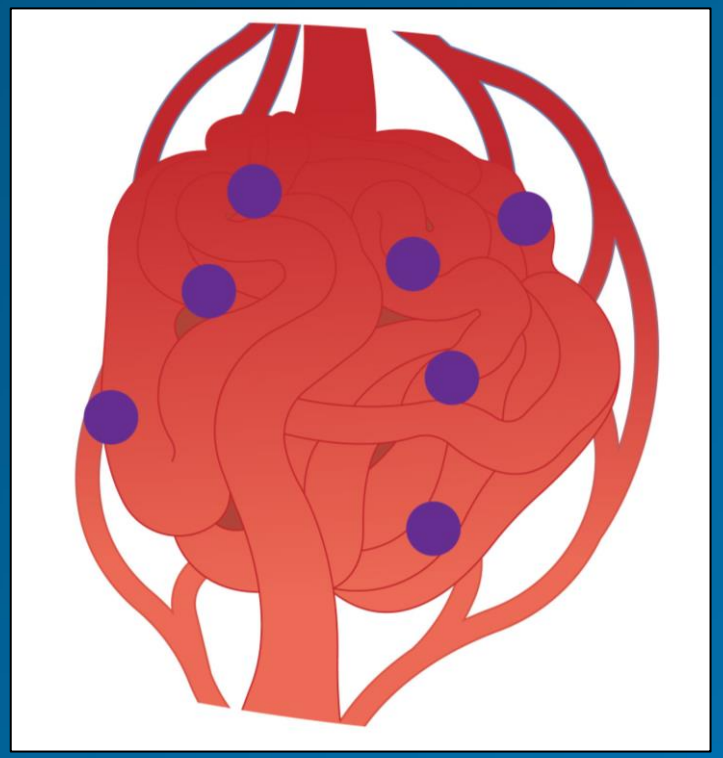
Infectious
- Cellulitis
- Bacteremia

Abnormal lymphatics
- Lymphedema
- Cutaneous lymphatic lesions
- Lymphatic leak
  - Chylous effusion
  - Chylous ascites

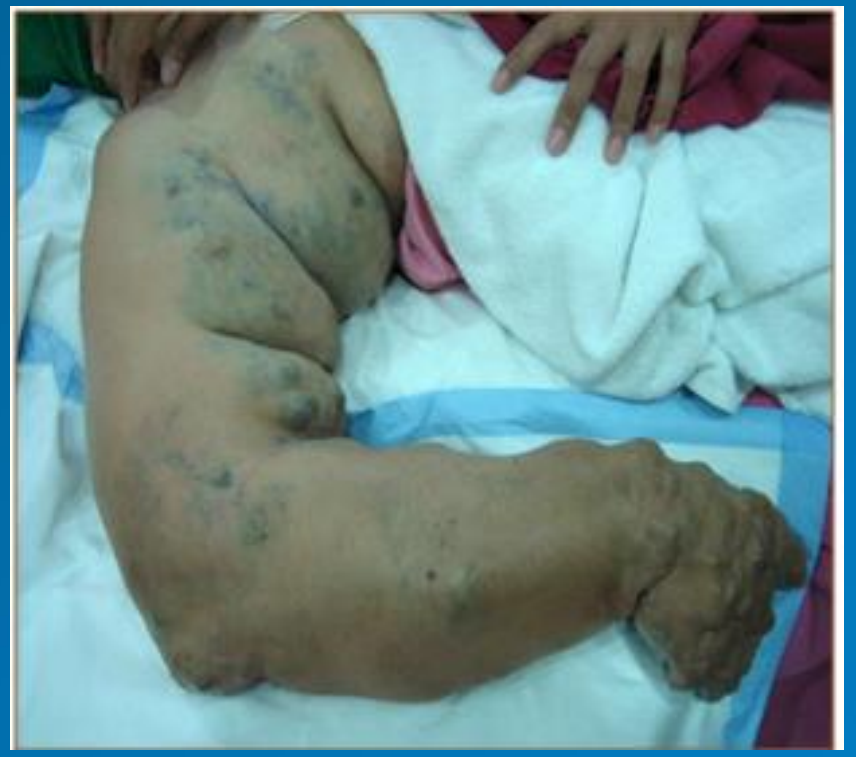
Pain

GI, gastrointestinal; PROS, PIK3CA-related overgrowth syndrome.

Local Intravascular Coagulopathy



Phleboliths



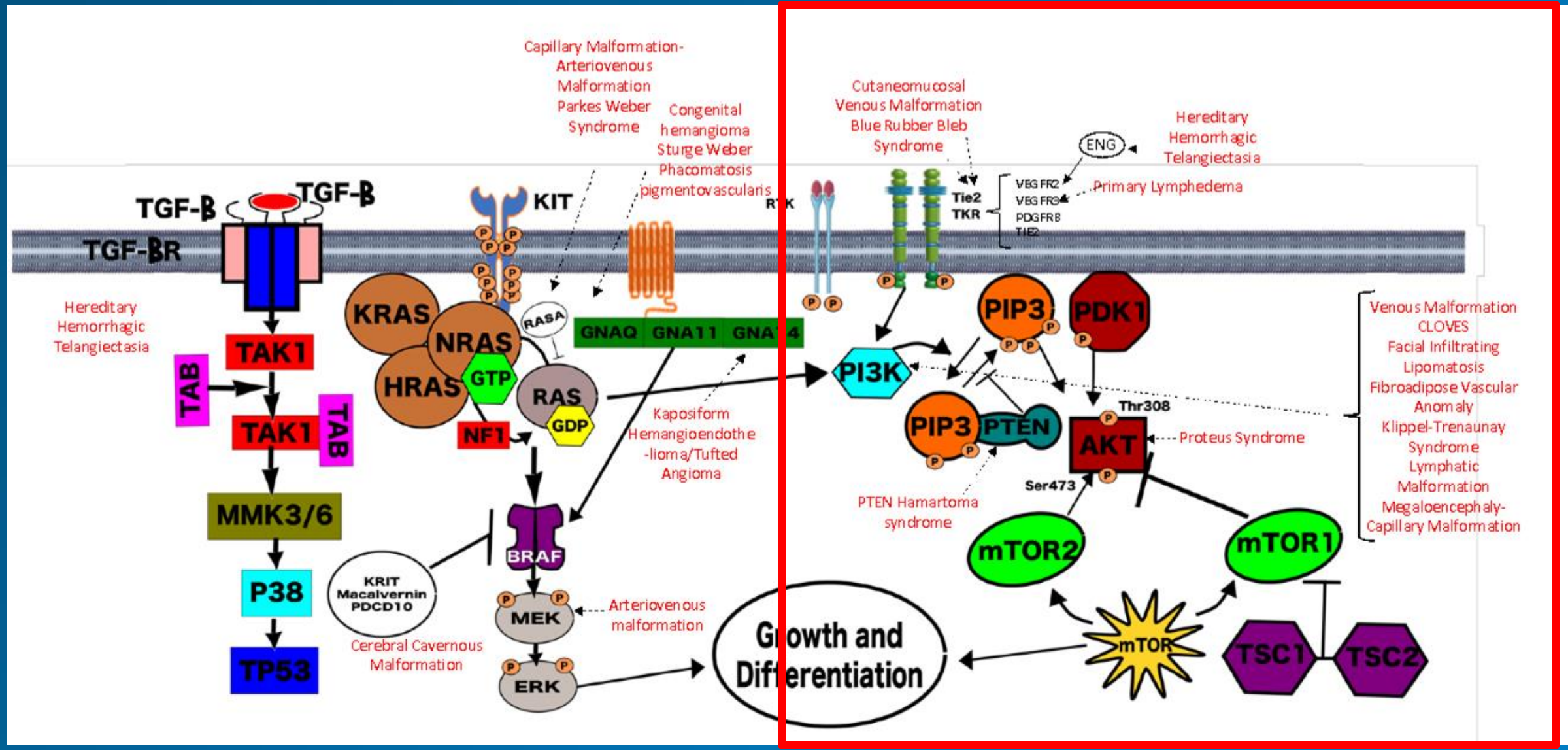
Churojana. *Pharm Pharrmacol Int J*. 2020;8(1):38-40. © Churojana 2020.

Difficulties in Making the Diagnosis

- Overlapping features
- Lack of consensus
  - Even among and between clinicians, radiologists and pathologists
- Genetics?
  - Historically a clinical, radiographic, and/or pathologic diagnosis
  - A “renaissance” of genetic understanding in the past decade
  - All patients with PROS phenotypes but may just be “ROS” with different or unknown genetic underpinnings

PROS, PIK3CA-related overgrowth syndrome.

Genetic Pathways Implicated in Vascular Anomalies



CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal abnormalities.

Borst et al. *Front Pediatr*. 2020;8:579591.

What Is PIK3CA-Related Overgrowth Spectrum?

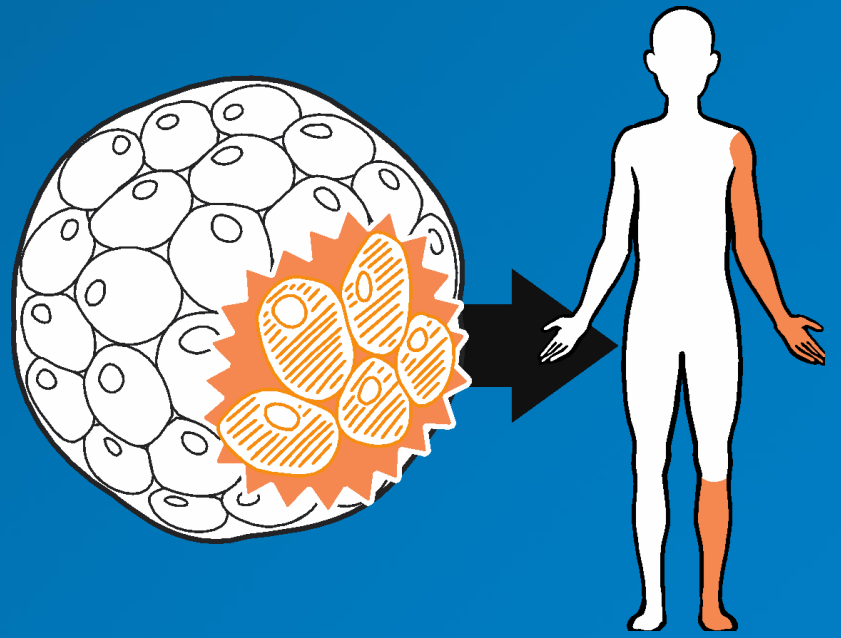
A mosaic expression of a diverse phenotype of vascular anomalies and tissue overgrowth driven by somatic, gain-of-function mutations in the *PIK3CA* gene

SOMATIC

Acquired, postzygotic, early developmental mutation

MOSAIC

Interindividual phenotypic heterogeneity
Asymmetric overgrowth (adipose tissue, muscle, skin, bone, blood or lymph vessel, neural tissue)



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Approach to Genetic Testing

- Sample involved tissue
- Targeted next-generation sequencing panel
- Optimize molecular diagnostic approach to detect low-level mosaic variants
  - Allelic frequency as low as 5% or even 1%
- Consider reevaluation of sample and testing quality if unexpected results

Sanger method

sequences a single DNA fragment at a time

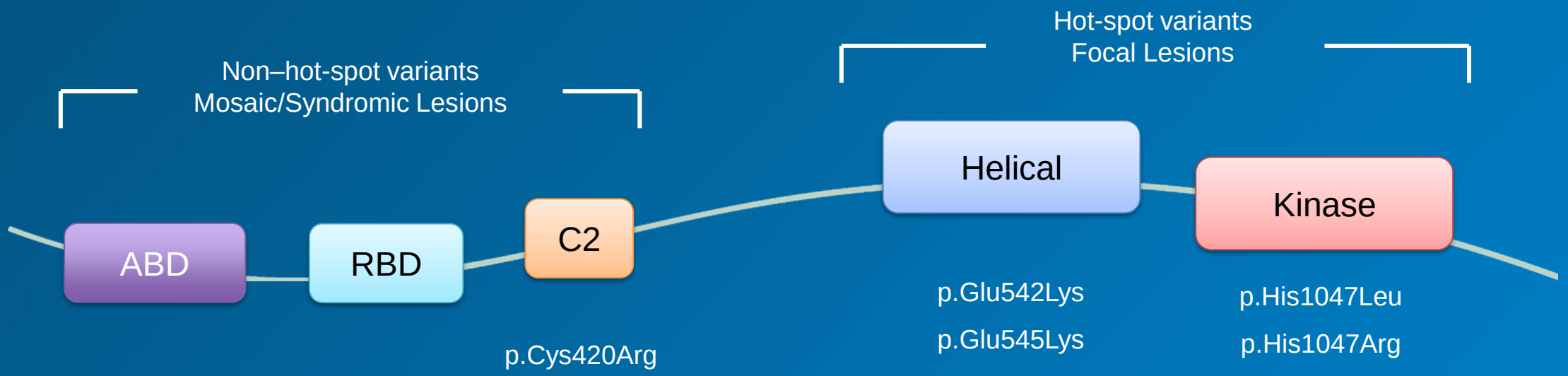
Next-Generation Sequencing

is massively parallel, sequencing millions of fragments simultaneously per run.

Can sequence hundreds to thousands of genes at one time or a more limited panel.

Greater discovery power to detect novel or rare variants with deep sequencing

PIK3CA Gene: 3q26.32



84% of identified pathogenic *PIK3CA* variants in PROS are "hot-spot" variants

Somatic variant profile similar to that of cancer

77% of pathologic variants were detected at <10% allele frequency

PROS, PIK3CA-related overgrowth syndrome.
Courtesy of Taizo Nakano, MD.

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Traditional Therapies for PROS

Supportive Care

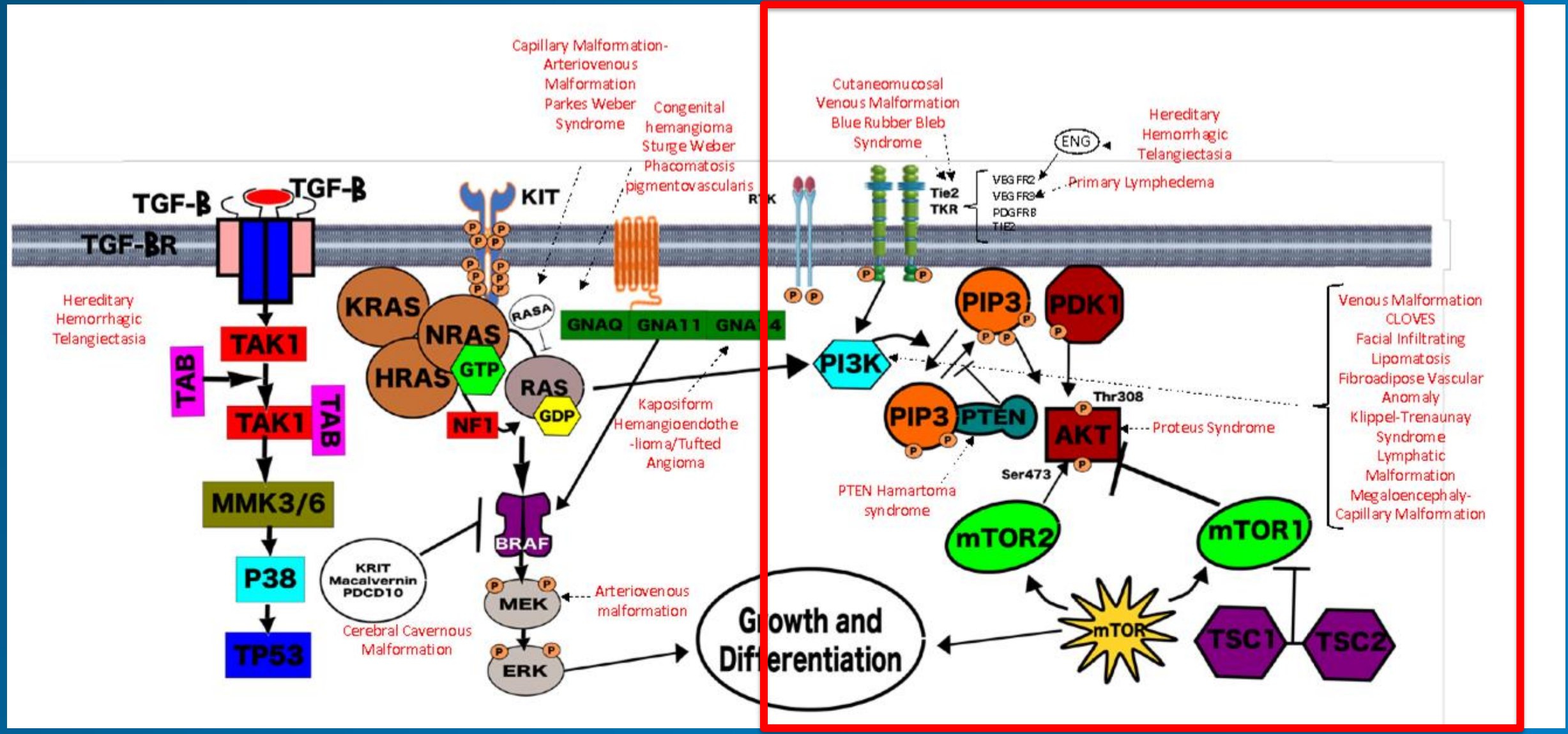
- Anticoagulation
- Compression garments
- Decompression massage
- Nutrition
- Pain medication
- Psychologic support

Procedural Intervention

- Surgery
  - Surgical resection
- Interventional Radiology
  - Sclerotherapy
  - Cryotherapy
  - Embolization

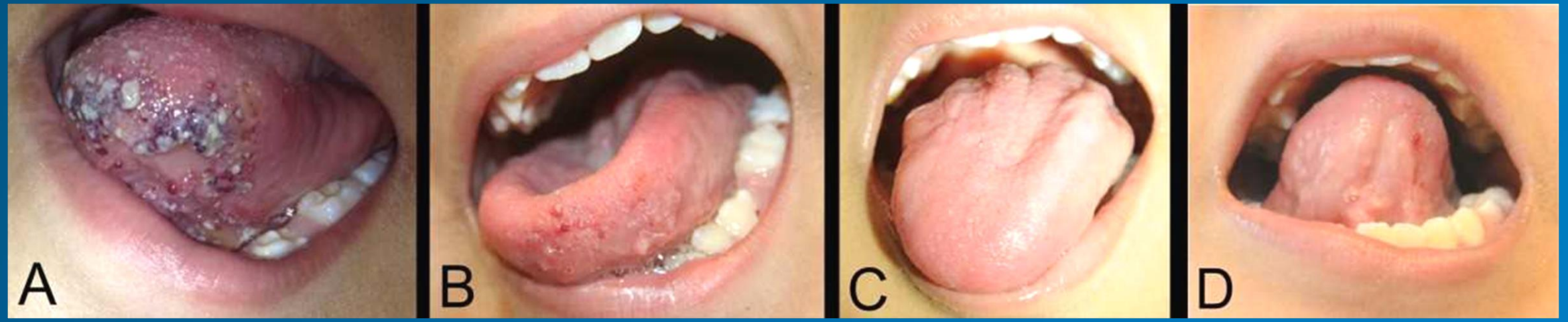
PROS, PIK3CA-related overgrowth syndrome.

Genetic Pathways Implicated in Vascular Anomalies



Borst et al. *Front Pediatr*. 2020;8:579591.

Sirolimus



Adams et al. *Pediatrics* 2016;37:e20153257.

Sirolimus: PROMISE and VASE Trials

Phase 2 PROMISE trial

- Efficacy and safety of 26 weeks of low-dose sirolimus in 30 patients with PROS disorders
  - Mean total daily dose: 1.2 mg once daily adults; 0.58 mg twice daily children
  - Mean percentage tissue volume reduction: -7.2% (*P*=0.04) at affected sites but not in unaffected areas (*P*=0.48)
  - 72% of participants experienced ≥1 adverse event related to sirolimus
    - 37% were grade 3 or 4 in severity
    - 18% study withdrawal rate
  - Although low-dose sirolimus prevented progressive overgrowth of fatty tissue, it did not decrease existing overgrowth

Phase 3 VASE trial

- Evaluating the efficacy and safety of sirolimus in the treatment of vascular anomalies that are refractory to standard care (NCT02638389)

Parker et al. *Genet Med*. May 2019;21(5):1189-1198; Van Damme, et al. *Am J Clin Dermatol*. Oct 2020;21(5):657-668; Seront et al. *Curr Opin Hematol*. May 2019;26(3):185-192; Dong et al. *Medicine (Baltimore)*. 2020;99(40).

Targeted Therapies: Vascular Malformations

Gene Target	Drug	Route	Clinicaltrials.gov	Status	Other use
PIK3CA	Alpelisib	po		Recruiting	Breast
				Closed **FDA Approved**	
	VT30	Topical		Closed / stopped	
AKT	Miransertib	po	NCT03094832 NCT04980872	Closed / stopped	Melanoma, SCLC, Thyroid cancer
MEK	Trametinib	po			Adult Cancers

FDA, US Food & Drug Administration; po, orally; SCLC, small cell lung cancer.

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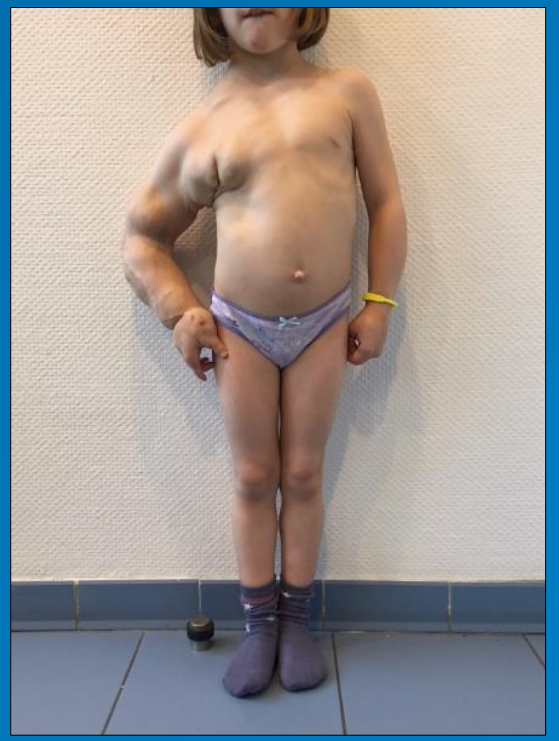
Alpelisib

Targeted therapy in patients with PIK3CA-related overgrowth syndrome

- French study in 2018
- Oral PIK3CA inhibitor
- All patients had documented clinical responses
- Well-tolerated



Venot et al. *Nature* 2018;558(7711):540-546.

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Alpelisib: EPIK-P1 Trial

Real-world evidence from a retrospective chart review study

- Primary objective: assess efficacy by the proportion of responders (pts with ≥20% reduction from tx start in the sum of target lesion volume) at week 24
- Reduced target lesion volume and improvement in PROS-related symptoms and manifestations
- 12/32 (37.5%) met primary endpoint
- 74% of patients with imaging at baseline experienced some reduction in sum of target lesion volume, with a mean reduction of 13.7% at Week 24
- At week 24, investigators observed patient improvements in pain (90%), fatigue (76%), vascular malformation (79%), limb asymmetry (69%), and disseminated intravascular coagulation (55%)
- Most common AEs of any grade: diarrhea (16%), stomatitis (16%), hyperglycemia (12%)
- Most common grade 3/4 AE was cellulitis (4%)

First FDA-approved treatment for PROS

April 2022: FDA accelerated approval for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PROS

AE, adverse evemt; FDA, US Food & Drug Administration; PROS, PIK3CA-related overgrowth syndrome.
Canaud et al. Annals of Oncology. 2021;32:S1297.

Alpelisib: EPIK-P2 and EPIK-P3 Trials

Phase 2 EPIK-P3 trial

- Assessing long-term safety and efficacy of alpelisib in patients with PROS who previously participated in EPIK-P1 (NCT04980833)

Phase 2 EPIK-P2 trial

- Assessing efficacy, safety, and pharmacokinetics of alpelisib in pediatric and adult patients with PROS (NCT04589650)
  - Approximately 174 patients enrolled in 2 groups (adult ages ≥18 years and pediatric ages 6-17 years) will be randomized 2:1 to daily oral alpelisib or matching placebo
  - Primary objective: demonstrate the efficacy of alpelisib, defined as ≥20% volume reduction in the symptomatic target lesion(s) per BIRC, at Week 24 in each group

BIRC, blinded independent review committee; PROS, PIK3CA-related overgrowth syndrome.

Canaud et al. *Journal of Clinical Oncology.* 2021. DOI: 10.1200/JCO.2021.39.15_suppl.TPS3160 Journal of Clinical Oncology 39, no. 15_suppl.

Clinical Case

Born with spinal defects, abdominal lymphatic malformations, right foot deformity, hemimegalencephaly complicated by seizures

- Underwent hemispherectomy and ventriculoperitoneal shunt placement for intractable epilepsy in infancy
- Demonstrated progressive facial and extremity asymmetry, overgrowth
- Multiple rounds of surgical debulking of lipomatous overgrowth resulted in disease re-expansion
- *PIK3CA* variant identified from involved tissue

Suggestions for Changes in Practice

- Take a look at ISSVA.org and remember this URL when seeing children with vascular anomalies in the office
- Take a detailed history when seeing patients to establish where they are and where they will likely go:
  - Consider filing or having parents save serial photos
- Multidisciplinary dedicated vascular anomalies clinic
- Consider QoL issues
- Consider family preference
- Direct patients to support groups
- While there are currently no consensus guidelines for PROS, practice trends are changing rapidly

PROS, PIK3CA-related overgrowth syndrome; QoL, quality of life.

Thank You

Thank you for participating in this activity!

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