

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

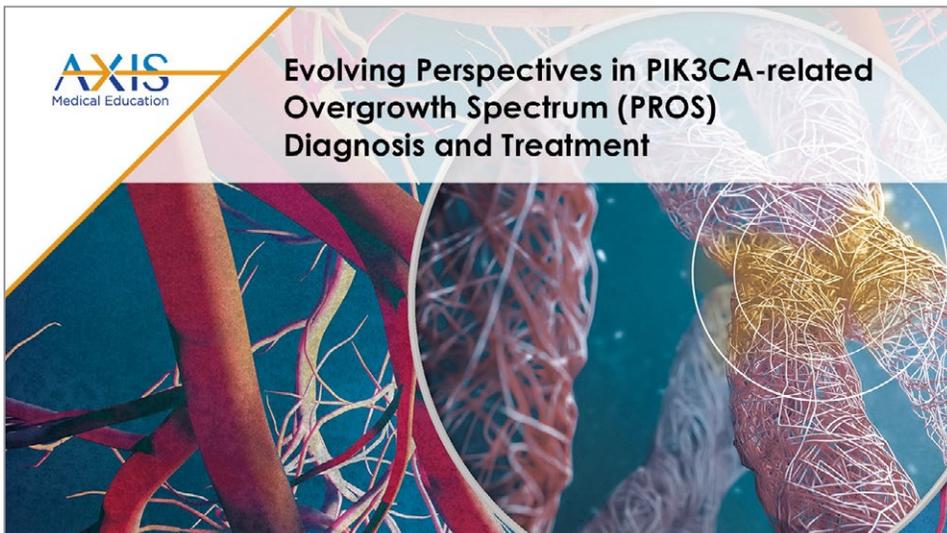
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Evolving Perspectives in PIK3CA-related Overgrowth Spectrum (PROS) Diagnosis and Treatment

Julie Blatt, MD and Taizo Nakano, MD



- ▶ **Dr. Mencia (Moderator):** Welcome to CME on ReachMD. I'm your host, Dr. William Mencia, Vice President of Scientific Affairs for Global Learning Collaborative.

Faculty Panel Introductions

Julie Blatt, MD

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- ▶ Joining me are Dr. Julie Blatt and Dr. Taizo Nakano.
Dr. Blatt is Co-Director of the Vascular Anomalies Center and Professor of Pediatric Hematology-Oncology at the University of North Carolina in Chapel Hill. Dr. Blatt, thank you for being with us today.

Dr. Blatt: Glad to be here.

Dr. Mencia: Dr. Nakano is Medical Director of the Vascular Anomalies Center, and Associate Professor of Pediatrics-Hematology/Oncology and Bone Marrow Transplantation at Children's Hospital of Colorado. Dr. Nakano, it's great to have you with us.

Dr. Nakano: I appreciate the invitation. Great to be here.



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Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

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► **Dr. Mencia:** First, a disclaimer and disclosures that we may be discussing off-label use of approved agents or agents that are in development.

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



► And the learning objectives for today's activity.

Moderator: It's known that PIK3CA-related overgrowth spectrum, or PROS, is a group of disorders that are characterized by clinical diagnostic criteria as well as genetic criteria. Can you expand on these criteria? And which of these factors do you feel are most clinically significant?

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.

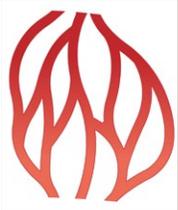
Overview table

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

* 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.

► **Dr. Blatt:** Before we can talk about PROS, it's important to establish some definitions to make sure we're all on the same page.

The International Society for the Study of Vascular Anomalies, ISSVA, divides vascular anomalies into vascular tumors, things like hemangiomas, which we won't be talking about, and vascular malformations. Now, conceptually normal vessels are straight. Veins, arteries, and capillaries carry blood, and lymphatics carry lymph or chyle. Vascular malformations are abnormally formed, snake-like vessels. And this changes the flow characteristics and leads to problems as we'll outline.

Vascular malformations can be composed of one or more types of vessels as shown in the ISSVA schema. Early on, vascular malformation syndromes were classified by phenotype based on physical examination and radiographic evaluation to define the vessel involvement. So by way of further introduction to PROS, we'll run through a few pictures of patients who illustrate some of the findings and spectrum of these disorders.

Klippel Trenaunay Syndrome: CLVM

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



CLVM, capillary lymphatic venous malformation.

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▶ We'll start with Klippel-Trenaunay syndrome, KTS, otherwise known as CVLM, capillary venous lymphatic malformation—the prototype for PROS. It's characterized by hemihypertrophy or overgrowth. There are capillary malformations usually, but not always in the area of overgrowth. Underlying all of that, there's usually a vascular malformation that can be venous, lymphatic, or more usually a veno-lymphatic combination malformation. You can also note these blips pooing out from the vascular malformation, signaling an underlying lymphatic component.

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 abnormalities.

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▶ Another example of PROS is CLOVES. This was originally clumped with KTS, but is now recognized as distinctive in its own subset of PROS. It's relatively rare, fewer than 200 cases have been reported to date. Although I think this is an underestimate. But contrast with something like 15,000 cases of KTS patients in the U.S. CLOVES is an acronym for congenital lipomatous overgrowth, which overgrowth can also be musculoskeletal, vascular malformations, epidermoid nevi, and the S is scoliosis, skeletal, and spinal problems. Some of those spinal problems are actually arteriovenous malformations. I do want to point out the sandal gap toe deformities, which are characteristic although not pathognomonic.

Although all PROS are thought to be congenital, they're not always obvious at birth. The natural history of most vascular malformations is one of proportionate growth during childhood until around puberty when the vascular malformations, in particular, the overgrowth, to some extent grow disproportionately. In women, there's a similar bump at the time of pregnancy.

MCAP Syndrome



- Megalencephaly
- Capillary malformation

MCAP, megalencephaly-capillary malformation polymicrogyria.

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▶ Third example that we'll show is MCAP, megalencephaly capillary malformation syndrome. That's characterized by macrocephaly, which is really a surrogate for the megalencephaly that figures prominently in a number of PROS syndromes. In addition to the macrocephaly, MCAP is characterized by this midline facial capillary malformation, which you can see, and often with associated neurologic problems.

These three examples are a quick introduction to the diversity of phenotypes, which in turn, results in diversity of morbidities.

PIK3CA-Related Overgrowth Syndromes

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

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

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.

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▶ Finally, we come to a definition of PROS. We'll come back to PIK3CA-relatedness in great detail, that's the P. Overgrowth, which again is lipomatous, as well as musculoskeletal. And the syndrome is also associated with PIK3C-related vascular malformations. And PIK3C-related nonvascular lesions, which are often involved—skin involvement, as well as sometimes involvement of other underlying organs, such as in this case, focal cortical dysplasia of the brain.

This is a very heterogeneous group of diseases. In addition to KTS, CLOVES, and MCAP that we've talked about, there's this other alphabet soup of acronyms, which I've listed only to give you an idea for how variable these things can be. They can be as simple as macrodactyly as an isolated finding to many problems that are seen in CLOVES and some of these other problems. Some of them are easy to recognize, and others may require input from a multidisciplinary team that includes us in

pediatric hematology/oncology, dermatology, genetics, radiology, sometimes pathology, and we draw in other subspecialists as needed.

This is a classification that continues to evolve, and I suspect in the next couple of years that we'll be seeing a much longer list.

So Taizo, maybe you can tell us something about the problems these patients face?

Complications of PROS

Psychological

Anxiety
Depression

Neurodevelopmental

Megalencephaly
Seizures
Cognitive changes

Organ abnormalities

Pulmonary
GI
Hepatic
Renal
Cardiac

Functional impairment

Soft-tissue overgrowth
Orthopedic
Muscular
Central and peripheral nervous system

Coagulopathies

Thrombophilia
Hemorrhagic

Cardiovascular

Orthostatic
Hypotension

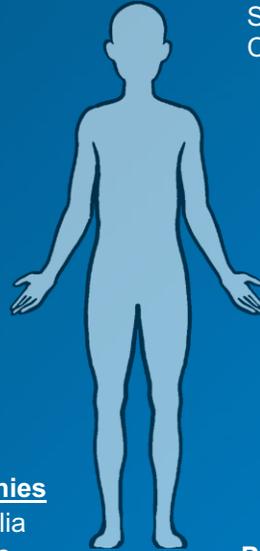
Infectious

Cellulitis
Bacteremia

Abnormal lymphatics

Lymphedema
Cutaneous lymphatic lesions
Lymphatic leak
Chylous effusion
Chylous ascites

Pain



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

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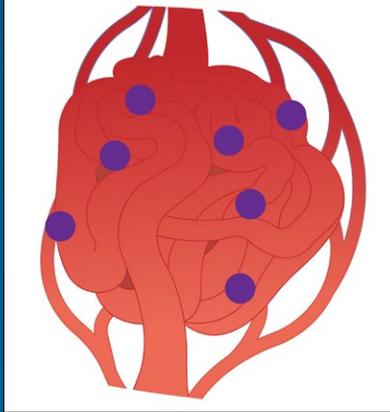
► **Dr. Nakano:** That was a really great background. I appreciate the opportunity to expand not just on the physical presentation of PROS conditions, but the functional impact of these diseases as well. And, it's not necessarily talking about criteria, but functional phenotyping. The impact of disease, which is important.

As Julie mentioned, no system is really spared. But when

you think of the diversity of patients involved, and their neurocognitive and neurodevelopmental systems, they're organ developments that are impacted and can have complications. I'm particularly sensitive as a hematologist to vessel complications, both blood vessels and lymphatics. Julie mentioned issues with lymphatics. Well, lymphatic leaks can be

particularly troublesome, and coagulopathies can be life-threatening. It's hard to judge patient to patient, what you would consider severity of disease after all. Pain, as a complication of disease could be severe. Seizures that are intractable could be severe. Any one of these conditions, if they're bad enough, can be complicated enough to be severe disease.

Local Intravascular Coagulopathy



Phleboliths



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

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► My pitch is, and equal to the physical anomalies, the quality-of-life impact of these conditions. In and of itself, it's a sign, it's a symptom that needs to be judged in severity of disease and chronic pain. I'll persevere for a moment again. I can't help myself, hematologist - one particular complication of disease, coagulopathy. If you find yourself with a tangle of vessels, you can only

imagine that blood needs to keep moving. If it hits a traffic jam, if it doesn't flow well, blood is going to clot. The endothelium of these vessels is really different. They're very activated, and if you have clot, maybe locally, it's frustrating to have the chronic pain associated with little calcified clots called phleboliths. If there's a direct conduit to the deep venous

system, a direct connection from that malformation to the deep venous system, then you risk more life-threatening complications, you risk deep venous thrombosis and pulmonary embolism. That's significant morbidity and mortality just to convey the life-threatening nature of some of the complications of this disease.

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.

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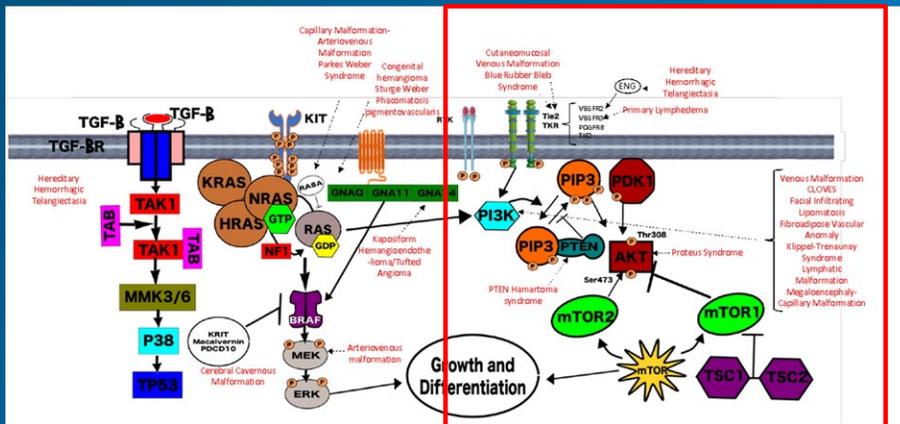
▶ Getting back to the question you asked about difficulties in making the diagnosis, it's not so easy, there are a lot of overlapping features. Now, just think how many subspecialties a patient could present to: dermatologic findings, masses that go to oncologists, surgeons. They're going to be diagnosed differently, treated differently, depending on the subspecialty they may present to. Even within those subspecialties, think about the lack of consensus that exists right now in the field, that

there's very few prospective natural history studies that tell us the outcome of these conditions. And so, we've evolved in our diagnostic tools nowadays to involve not just a clinical diagnosis with phenotyping, or even radiographic.

But to really get to a genetic diagnosis, that's really the reason Dr. Blatt and I got interested in this field, was to take and revolutionize this field, and have a molecular component to its diagnostic

abilities. There's certainly a renaissance of molecular genetics that's redefining vascular anomalies right now, and changing names from conditions like CLOVES and MCM that were mentioned, to PIK3CA variants named after the molecular defect they're diagnosed after. Now's the time to change diagnosed vascular anomalies by genetic variants that drive this dynamic activity that they have. You need to talk about genetic pathways or protein pathways.

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.

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► We can now define several vascular anomalies by the genetic defects, and in the signaling cascade represented in this slide. These are signaling cascades related to angiogenesis and growth, and increased metabolism. And the focus today will just be on those involved with PI3K, which is protein encoded by *PIK3CA*. We'll use those terms interchangeably.

Just be amazed at how many vascular anomalies have been associated with proteins on this pathway. These are defects that increase the function of that growth, that metabolism. It's really the key to unlocking the pathophysiology of disease here. This is a preview of this renaissance of molecular genetics in the field.

Moderator: Thank you for that comprehensive overview, especially as we understand the genetic component of PROS. We know that some of these somatic activating mutations of *PIK3CA* can cause a series of heterogeneous changes in a patient. These changes are wide ranging. Can you explain for us the importance of utilizing next-generation sequencing versus other methodologies for the molecular diagnosis of these disorders of PROS? And what are the clinical indicators that you get from the sequencing data?

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

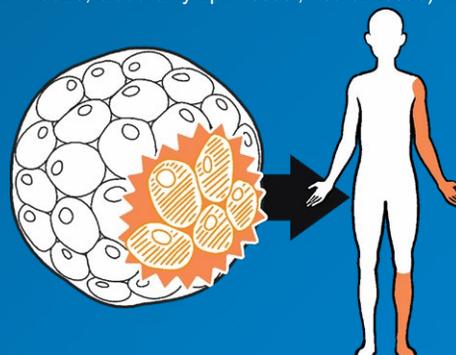
SOMATIC

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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► **Dr. Nakano:** These are really great questions. I'm really glad to have the opportunity to provide maybe a little bit of background before we get into the actual genetic testing, some terminology that I think will be helpful. Before I send a genetic test with a family, I think that this can be sometimes a scary subject and some terms need to be defined to help them get grasp what we're going after. Although some medical conditions are germline, and therefore, heritable from a mother and father, these PROS conditions are somatic, acquired.

A somatic condition is acquired genetic insult that happens early in development. But this is not passed on from

the mother and father to the patient. This is not something that we expect the patient to pass on to their children. And again, that's where there's this scariness that gets involved that you really need to clarify. It's a somatic variant in a select number of tissues that was acquired after the sperm and egg came together.

The second term I would put out there is mosaic. This variant only impacted a select number of cells. There was an asymmetric pattern and asymmetric growth of that abnormal population of cells, in a mosaic distribution around the body. Different areas of the body may be impacted, but not all.

Lastly, the term I would describe as gain of function, so that the insult that the cells have undergone have increased activity, increased growth, increased angiogenesis, increased metabolic activity. And so, within an acquired somatic variant in a mosaic distribution throughout the body is causing an overgrowth or increasing function of metabolic activity. That's a nice foundation to give families before you even ask them to undergo testing.

Dr. Blatt, maybe you could give us a background on how you would approach genetic testing for these conditions.

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

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► **Dr. Blatt:** Not everybody needs testing or needs testing off the bat. Although genetic testing is often helpful for confirmation of diagnosis and for treatment. However, I think all of us would agree that phenotype trumps genotype, and sometimes we have a patient with PROS who has not been tested, or who doesn't even have a *PIK3CA* mutation. So having said that, most patients are offered genetic testing at some point.

The way we go about getting tissue is summarized on the left. That's important to get tissue that's involved because these gene mutations are somatically or mosaically expressed; they're only present in some tissue. Often, getting that tissue is as easy as a punch biopsy or skin biopsy of a capillary malformation. Sometimes it requires a bigger surgical biopsy.

A current area of research is using cell-free DNA from blood or lymph to do testing but that is not commercially available just yet.

Once we get tissue, we have to know what to ask for. And sometimes we'll ask for a single gene, such as gene to just look for *PIK3CA* mutations.

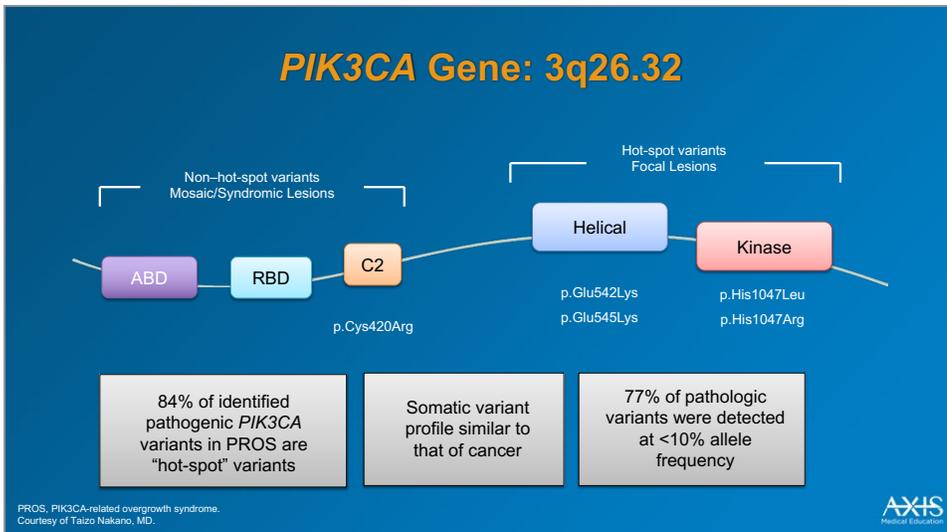
And sometimes we'll ask the lab to do a complete panel that is *PIK3CA* as well as other genes in its signaling pathway. And sometimes we'll look for the pathways that Taizo did not emphasize but can be important in our vascular malformation syndromes. We want to optimize testing based on cost as much as other things, but also to look for the very low frequency of these allelic mutations, which can be in as few as 1% of cells in a sample that's given to the laboratory.

Now the other thing we want to do is know what testing is around. There are two methods that are invoked for genetic testing right now. One is the Sanger method, which sequences a single DNA fragment at a time. The next one, which we hear a lot about is next-generation sequencing, or NGS. And that has the advantage of being able to sequence hundreds or even thousands of genes at one time. Although we often use it for more limited panel. One of the things we like to do with it even for a single gene or small panel of genes, is deep sequencing. That's just the way of looking at large numbers of

cells, because sometimes the samples that we give to the lab don't have too many cells that are involved with the mutation. So we have to use something that can look at very large numbers of cells to optimize things.

Fortunately, I've got to say that neither Taizo nor I are the ones who are the arbiters of what testing is used. That's the laboratory. Although it's worth knowing this terminology, that really has very little to do with us on a day-to-day basis.

Once in a while we get back from the lab, even after all of this, an answer that is not helpful. Either there's not a mutation at all, or the mutation is something other than what we expected. And what we do have to do is to consider whether we need to ask the lab to reevaluate either the same sample, whether we need to rebiopsy a patient, or once in a blue moon, we go to a different laboratory. A lot of these decisions don't have anything to do with us either; they reside with the insurance companies because these are very expensive tests and sometimes we do have limitations.



▶ Most phenotypic PROS patients will have *PIK3CA* mutations. And *PIK3CA* is a gene that's present on chromosome 3. The vast majority of pathogenic *PIK3CA* variants, about 85% of them, occur in limited areas called hotspots. Interestingly, these hotspots are the same hotspots seen in adult cancers, things like breast cancer or melanoma. But unlike the clonal expansion that is seen in cancers, these mutations are present in relatively small numbers of cells. Cancers may have 80% or 90% of cells expressing the mutation, that's not the case in our patients. And that again emphasizes the need to do NGS.

Moderator: Today, PROS treatment has been limited primarily then to managing its clinical manifestations, usually involving endovascular surgical procedures. But we know that these procedures don't eliminate the frequent regrowth that we see in PROS. Unfortunately, that means multiple surgeries for our patients. So, can you go through some potential treatments that may currently be under investigation and the impact that these treatments might have on these patients with PROS? I'm also curious as to your perspective as to how far along these agents are? As they become available, where can we expect them to be used in terms of sequencing?

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.

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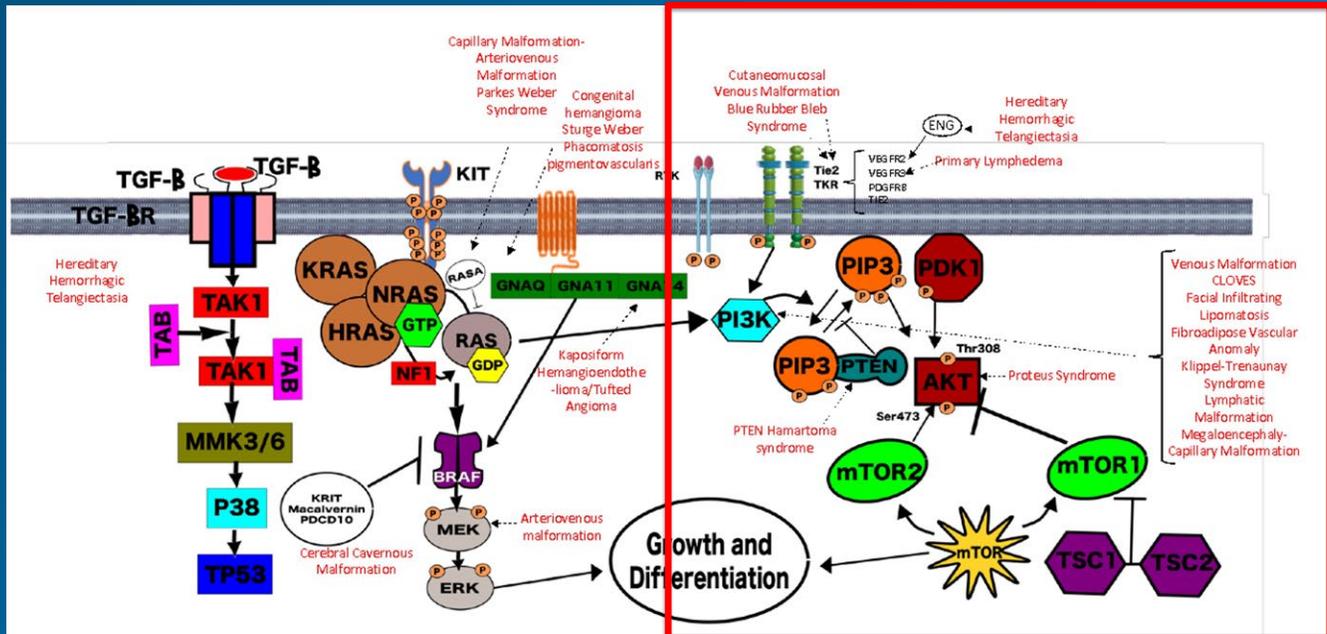
► **Dr. Blatt:** It's important to remember some of the issues that you talked about already, which is that there are interventions that have been used historically to treat PROS, but they continue to be important, and they have nothing to do with genetics. That includes supportive care, which I've listed alphabetically, anticoagulation to take care of the problem of localized

intralesional coagulation that Taizo mentioned before. Compression garments, decompression massage, nutrition, other pain medications, psychologic support. The procedural interventions remain at the forefront of treatment that includes surgery, both for biopsy, for resection, or debulking. And vascular interventional radiology where

our VIR colleagues may put in a catheter and inject some stuff that causes the lesions to shrink down. Sometimes it freezes them.

Importantly, none of these is curative. Even with surgery, these things grow back. This has pushed all of us to think about better treatment options.

Genetic Pathways Implicated in Vascular Anomalies



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

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▶ Going back to the slide that Taizo showed before, the emphasis for the past 10 years or so has been finding drugs that target pathogenic genes. We hope that such treatment will be the answer. This is where PIK3CA, the P of PROS, becomes so important. In truth, however,

we've been targeting this pathway for a long time, even before we knew that PIK3CA was the driver. The initial focus was really on mTOR at the bottom of the pathway. And so sirolimus is a PTEN or end mTOR inhibitor. It's an oral drug that's been used for decades as an

immunosuppressant to prevent rejection in organ transplant patients. Through some fortuitous observations, it was found to be helpful in vascular malformations and has really been the core of treatment of vascular anomalies, both malformations and some vascular tumors since 2008.

Sirolimus



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

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▶ This is a picture from an early relatively early phase 2 study by Denise Adams and her colleagues at Cincinnati Children's Hospital. It shows a patient from that study who had a lymphatic malformation of his tongue. You can see these lymphatic blebs coming out here, and you can imagine how painful they must be. That patient was started on sirolimus. And within a couple of weeks or a couple of months at most, many of these started to go away, the patient began to feel better, and over time they went away completely.

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).

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▶ Since that time, there have been other clinical trials to look at the efficacy and safety of sirolimus. PROMISE is one trial that looked at low-dose sirolimus for 6 months. That confirmed its effectiveness, but also pointed out some inadequacies and additional side effects that we did not know about.

The VASE trial, vascular anomalies sirolimus in Europe is a phase 3 trial, and it's ongoing. It's important that sirolimus sometimes shrinks vascular malformations quite a bit, but a lot of times it doesn't; it shrinks it a small amount. It's helpful with the overgrowth up to a point, but at very best, it does not cause regression of the overgrowth for the most part, so the search for ongoing drugs goes on.

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.



▶ On this slide, we summarize some vascular malformation targets and therapies that are in use, that are being developed. The gene that we've been most focused on is *PIK3CA*. The drug that clearly is at the forefront right now is alpelisib. Like sirolimus, it's an oral medication. And there are ongoing clinical trials that Taizo and I are part of, we'll be talking about those in a minute. Interestingly, over the past couple of months, alpelisib has been FDA approved for patients with

PROS, even when they have not had documentation of a genetic abnormality.

The field also includes other *PIK3CA* inhibitors. VT30 was a topical preparation that was in a trial that's now been closed and stopped. I'll get back to that in a minute. There are other genes and other pathways that we and others are trying to target. AKT is targeted by a drug called miransertib, also oral, and was in several clinical trials that have now been aborted. MEK is targeted by

trametinib. This is a drug that we use frequently, both in adult cancers and in pediatric cancers. We're struggling to start up some clinical trials in pediatrics.

These trials have been hard to fund. They have to be multicentered because these are relatively rare entities, and that's been difficult.

So maybe, Taizo, I can ask you to talk a little bit more about alpelisib to give the audience an idea about where our success lies at this point.

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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► **Dr. Nakano:** Yeah, I'd be happy to. I really appreciate the sirolimus story. It is truly one of the foundation—it's one of the most impactful stories of our generation in the field of hematology/oncology and its role in vascular anomalies.

The sirolimus story is the repurposing of drugs for vascular anomalies. Although it was great to target downstream of some of the variants we knew about, what we would love to do is target personalized medicine, right? Target the variant that you have. So if the story is PIK3CA, then the goal of personalized medicine would be to target

those variants. Alpelisib is an equally exciting story of drug repurposing. Here's a medication that already had FDA approval for the use in oncology primarily to treat adult breast cancers. And yet, it's a PIK3CA inhibitor.

Our colleagues in France carried out a pilot study to test the impact of this PIK3CA inhibitor on children with CLOVES and other PIK3CA-related overgrowth syndromes. And 19 patients were in this pilot study, and it had tremendously impactful results. There were clinical improvements in radiologic responses in all

patients documented. The intractable vascular tumors became smaller and heart conditions were improved. Hemihypertrophy was reduced and scoliosis attenuated. These were distributed internationally and really led to a buzz between physicians and families, needing to expand trials for this study.

This was the first study that provided evidence supporting PIK3CA inhibition as a promising strategy. It moved from supportive care and functional health to the actual thought of regression of disease, which is pretty amazing.

Alpelisib: EPIK-P1 Trial

Real-world evidence from a retrospective chart review study

- Primary objective: assess efficacy by the proportion of responders (pts with $\geq 20\%$ 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 event; FDA, US Food & Drug Administration; PROS, PIK3CA-related overgrowth syndrome. Canaud et al. *Annals of Oncology*. 2021;32:S1297.

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▶ The first study that was done was called the EPIK-P1 trial. This was a real-world retrospective collection of experience. It was a chart review experience of what patients had experienced on this medication beyond a pilot study. This is one that patients were looked at, they had experience on this medication for greater than 24 weeks, and they were looking for reduction in the size of lesions. As a target goal of reducing greater than 20% the size of

a lesion, 12 out of 32 patients demonstrated that goal. But interesting, 74% of those patients had some reduction in the size of the lesion.

This was a study that was looking at safety as well as efficacy, finding minimal impact on fatigue and some hyperglycemia that we've started to learn how to monitor. But as Julie alluded to, this culminated very recently in the FDA accelerated approval for the treatment of adults and pediatric patients greater than

2 years of age and older with severe manifestations of PROS with alpelisib.

This is really exciting for our field. I feel like the FDA approval of a PIK3CA-targeted medication for vascular anomalies is the single validation of our existence as hematology oncologists in this field to be able to target a lesion and produce a productive result is empowering.

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 $\geq 20\%$ 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. Cansud et al. *Journal of Clinical Oncology*. 2021. DOI: 10.1200/JCO.2021.39.15_suppl.TPS3160 *Journal of Clinical Oncology* 39, no. 15_suppl.

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▶ Right now, what's exciting is that there are a couple expanded trials to solidify this and give us the pharmacokinetics and data that we need to carry this medication further. The EPIK-P3 trial is simply the extension trial to the EPIK-P1 in patients that had been followed retrospectively are now following prospectively to continue to see what long-term impact of the condition can have.

In addition, and probably most importantly, is the EPIK-P2 trial, which both Julie and I have opened at our centers. This is the prospective efficacy and safety trial that we need for the PIK3CA inhibitor, alpelisib. It is exciting to take this trial forward and get the dosing and pharmacodynamics and pharmacokinetics that it is necessary to move this forward.

Moderator: That was certainly a very fascinating overview of the therapeutic approach. But could we take a moment to put this into the context of real patient care and maybe walk us through a patient case example?

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



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▶ **Dr. Nakano:** Most certainly. I happened to bring a case with me, one of my own patients to share with you all. This is Ellena. Ellena was born with spinal defects, had abdominal lymphatic malformations, and right foot deformity that needed an amputation eventually and hemi-megalencephaly that was complicated by epileptic seizures. Early in life, she underwent hemispherectomy and VP shunt placement for intractable epilepsy. She's 14 now, about to start high school and she's lived a life of progressive facial and extremity asymmetry and overgrowth. She has actually seen more than the average individual's share of surgical debulkings and lipomatous overgrowth resections that continue to re-expand and be re-resected. It is in this last decade that we've been able to diagnose her from a phenotypic diagnosis of

CLOVES to a molecular diagnosis of *PIK3CA* variant-related overgrowth condition.

But I would ask Dr. Blatt, how familiar does this story sound? And what do you think of the symptoms that need to be addressed when I talk about my patient here?

Dr. Blatt: I think Ellena is more severe than many patients. But she is typical of the complex multiorgan involvement that most of our PROS patients have. I think recognizing the spectrum of history and physical exam helps us make a diagnosis and plan diagnostic studies that includes bloodwork, radiographs, genetic studies. But a number of patients who develop signs and symptoms like Ellena's don't necessarily have them initially. It's important to realize that the manifestations evolve over time.

I suspect that some Ellena's problems weren't even present

or weren't appreciated at first, is that the case Taizo?

Dr. Nakano: That's correct. And yes, there was an evolution.

So, when I think of her care at our institution, and the multidisciplinary team that's had to care for her, I'm curious, Dr. Blatt, who would you recruit to be her team? Who do you think needs to be involved in the care of such a patient like this?

Dr. Blatt: This is clearly a multidisciplinary situation. Ellena certainly needed neurosurgery and neurology initially. At our center, we ask for help from our vascular interventional radiologists for her lymphatic malformation in her abdomen. In fact, our VIR docs see almost all of our PROS patients, and sclerotherapy remains a big part of things. In addition to neurosurgery, we'd enlist the help of other surgeons; plastic surgery for her face,

maybe for debulking of her back. And those are probably multidisciplinary, in addition, that is, ENT would probably help plastics. General pediatric surgery would help plastics looking at trying to debulk her back and such. Orthopedics for her feet, and other deformities, maybe orthotics. As a rule, even though we can make the diagnosis, we usually like to get genetics involved. You can see on the slide, the capillary malformation on the side, and interestingly, a lot of my patients find that to be the most distressing thing. So dermatology gets involved for laser therapy. So, this is multidisciplinary. And we don't want to forget about psychology, because body image is a big deal for these kids.

Dr. Nakano: In the last decade, I feel like her definition of disease has changed from a CLOVES community to a PIK3CA-related overgrowth community, and, I feel like a world of surgical and interventional history potentially moves to targeted therapy.

I may put you on the spot, Dr. Blatt, how would you treat her?

Dr. Blatt: In addition to the multidisciplinary approach into symptom management, drug therapy is big focus at most centers. It has evolved. A 14-year-old Like Ellena, when she first presented, would not have had many options or any options besides sirolimus. So I suspect she was treated with sirolimus. That's certainly how I would have treated her. A child like this might have some benefit from sirolimus. But it clearly is not going to be enough. And in 2022, alpelisib would be number one on our list, I suspect.

I am assuming that that's what's in the works, Taizo, is that right?

Dr. Nakano: I think the discussion has come up increasingly over the last year. This is an amazing rockstar kid who's about to start high school. A clinical trial schedule, or even the lab frequency schedule while on alpelisib, is actually the last thing from her mind, given that she's been able to embrace her diagnosis, embrace her condition, and become quite functional. It is in her generation that we're really excited for to offer the opportunity to have targeted therapy. This is a girl in a family

that's got their eye on the EPIK-P2 trial and they're really interested in seeing some of the safety data before moving forward. You and I will work hard to provide that for them. It's pretty exciting.

Dr. Blatt: The one thing I did want to add, Taizo, is that this is a good age to treat, because one thing we can't do is have somebody who's looking at pregnancy, beyond either sirolimus or alpelisib, or probably any of the other drugs that we can imagine. So, it's nice to get some control of disease before pregnancy.

Dr. Nakano: The other one that I would add to that is the fact that she's just started into puberty. We are well aware that during times of development with great hormonal change, we see exacerbations in underlying overgrowth conditions. I think it's very fair in my mind that I'm thinking of children, and the impact of this condition pre- versus post-puberty. That'll be something we'll have to study going forward.

Moderator: Let's wrap up our discussion today. If there's some key takeaways that you'd like to leave our audience with, what would those be?

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.

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► **Dr. Blatt:** Thank you for the opportunity to do that. When first seeing a patient, I like to remind myself of what diagnostic options are, and so I go to the ISSVA website, which is a summary for me. Certainly when I first started seeing patients like this, I used it frequently. I still continue to do that.

But in many respects, I think –that—as with many aspects of medicine—would go back to the basics. We want to take a detailed history, do a detailed physical exam, because these diseases are all-encompassing. We want to establish where a patient is and where they're likely to be going. It's helpful to know how involved a patient's disease is. Patients we think who are sick when we see them are going to continue to be sick. We don't necessarily know that. But patients who are let's say, preschoolers who might not be sick, we know that are getting closer to puberty and then pregnancy for the girls—the tempo of the disease may change.

I like to remind the parents that they can contribute by

taking serial photos of the kids; a lot of our families don't like to come in all the time, they live a distance. Even with telemedicine, it's often harder than just doing a physical exam in person. So serial photos do help.

And then the other thing I'd like to emphasize that most of us believe that these kids should be followed at some level in a multidisciplinary, dedicated vascular anomalies clinic. Now, that means different things at different centers. But in our center, we usually have patients see two or three of us, our vascular interventional radiologists and pediatric hematology oncology. Sometimes dermatology almost inevitably sees the patient all on the same day. Then we farm them out to other clinics as need be, so our surgeons, our radiologists, this kind of thing.

Dr. Nakano: For me it does come back to recognizing the importance of the functional impact, the quality of life of the patient. I would go so far as to say that the best outcome measure of any drug or any

medication or intervention we could do is the quality-of-life measure. Listen to the patient, listen to the family, in their own words. What is the impact of their condition? I think you'd be surprised how many aren't necessarily interested in a large area of tissue shrinking versus that the pain went away, that they were able to be more functional, mobile. These are the measures that if you work with families and family advocacy groups we hear over and over. I would encourage practitioners to really start finding measures even if it's formal, such as surveys, patient-reported outcome measures, that can give you an indication of how well you're doing in response to therapies that you choose to do.

I would give a shout out to the patient support groups who have really helped guide us in how we designed clinical trials, and how we advocate for patient's families. Guidelines for these diagnoses are not yet available. But they're coming, keep an eye out, they're in development.

Thank You

Thank you for participating in this activity!

▶ **Dr. Mencia:** Those are certainly some great comments for us to pause and reflect on as we come to the end of today's program. I want to thank my guests for helping us better understand PROS. Dr. Blatt, Dr. Nakano, it was great speaking with both of you today.

Dr. Blatt: Thanks for having us.

Dr. Nakano: Yes, pleasure to be here.

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